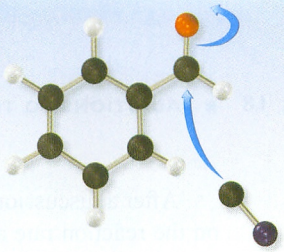
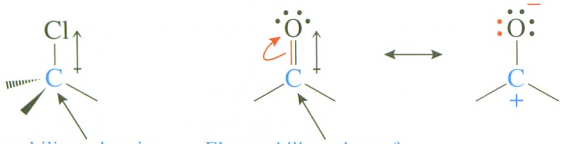


Additions to the Carbonyl Group

REACTIONS OF ALDEHYDES AND KETONES

CHAPTER 18

CHAPTER 8 DISCUSSED nucleophilic substitution reactions that occur at sp^3-hybridized carbons: the S_N1 and S_N2 reactions. In those reactions the nucleophile replaces a leaving group bonded to the electrophilic carbon. The carbon is electrophilic because the leaving group, being more electronegative, pulls the electrons of its bond with the carbon toward itself, making the carbon electron deficient. This chapter introduces a new electrophile, the carbon of a carbonyl group. This carbon is quite electrophilic because of the electronegativity of the oxygen of the carbonyl group. In addition, a charged resonance structure, where the pi electrons have moved onto the oxygen, makes a minor contribution to the structure of carbonyl-containing compounds and causes the carbonyl carbon to be even more electrophilic.



Electrophilic carbon in S_N1 and S_N2 reactions

Electrophilic carbon of the carbonyl group

The reactions presented in this chapter involve nucleophiles attacking at the electrophilic carbon of the carbonyl group of aldehydes and ketones. Chapter 19 discusses the reactions in which nucleophiles react at the carbonyl carbon of carboxylic acid derivatives.

MASTERING ORGANIC CHEMISTRY

- Predicting the Products of the Addition of Nucleophiles to Aldehydes and Ketones
- Predicting the Products of the Addition of Nucleophiles to α,β-Unsaturated Compounds
- Understanding the Mechanisms for These Reactions
- Predicting the Effect of the Structure of the Aldehyde or Ketone on the Position of the Equilibrium for These Reactions
- Using These Reactions to Synthesize Compounds
- Using Acetals as Protecting Groups in Organic Synthesis

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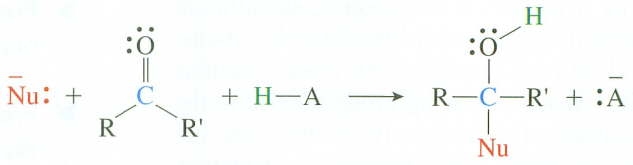
After a discussion of the general mechanisms for the reactions, the effect of structure on the reaction rate and equilibrium is presented. Then the reactions of various nucleophiles with aldehydes and ketones are discussed. Finally, a related reaction that occurs when the carbonyl group is conjugated with a CC double bond is considered.

18.1 General Mechanisms

The simplest version of these reactions results in the addition of the nucleophile to the carbonyl carbon and a proton to the oxygen, as illustrated in the following general equation:



The reaction stops at this stage with some nucleophiles, but with others it proceeds further to somewhat different products.

There are two mechanisms for this reaction that differ only in the order of Nu—C and O—H bond formation. Under acidic conditions—that is, in the presence of an acid that is strong enough to protonate the oxygen of the carbonyl group—the O—H bond is formed first. Under basic conditions—that is, in the absence of such an acid—the Nu—C bond is formed first. Each of these mechanisms is outlined in Figure 18.1.

Some of the nucleophiles that are employed in these reactions are quite strong bases, so the presence of even weak acids, such as water or ethanol, must be avoided. In these reactions a solvent that has no acidic hydrogens, such as diethyl ether, is used. The reaction follows the basic conditions mechanism and stops at the anionic stage until an acid is added during the workup. Reactions involving less basic nucleophiles can be conducted with water or alcohols as solvent. These reactions also follow the basic conditions mechanism with the solvent supplying the proton that is added to the negative oxygen in the second step. Reactions of even weaker nucleophiles that are also only weakly basic are conducted in the presence of acid, so the acidic conditions mechanism is followed. Protonation of the oxygen of the carbonyl group occurs first, making the carbon more electrophilic, thus facilitating the addition of the weak, neutral nucleophile in the second step.

Although these additions to CO double bonds have some superficial similarities to the electrophilic additions to CC double bonds that were presented in Chapter 11, there are many differences. The acidic conditions mechanism here resembles the mechanism for addition to carbon–carbon double bonds in that the electrophile (the proton) adds first, followed by addition of the nucleophile. However, in this case the first step is fast because it is a proton transfer involving oxygen, a simple acid–base reaction. The second step, the attack of the nucleophile, is the rate-determining step. (Recall that it is the first step, the addition of the electrophile, that is slow in the additions to CC double bonds.) Furthermore, in the case of additions to simple alkenes there is no mechanism comparable to the one that operates here under basic conditions, in which the nucleophile adds first. Because the nucleophile adds in the slow step, the reactions presented in this chapter are termed *nucleophilic additions,* even if the protonation occurs first. In

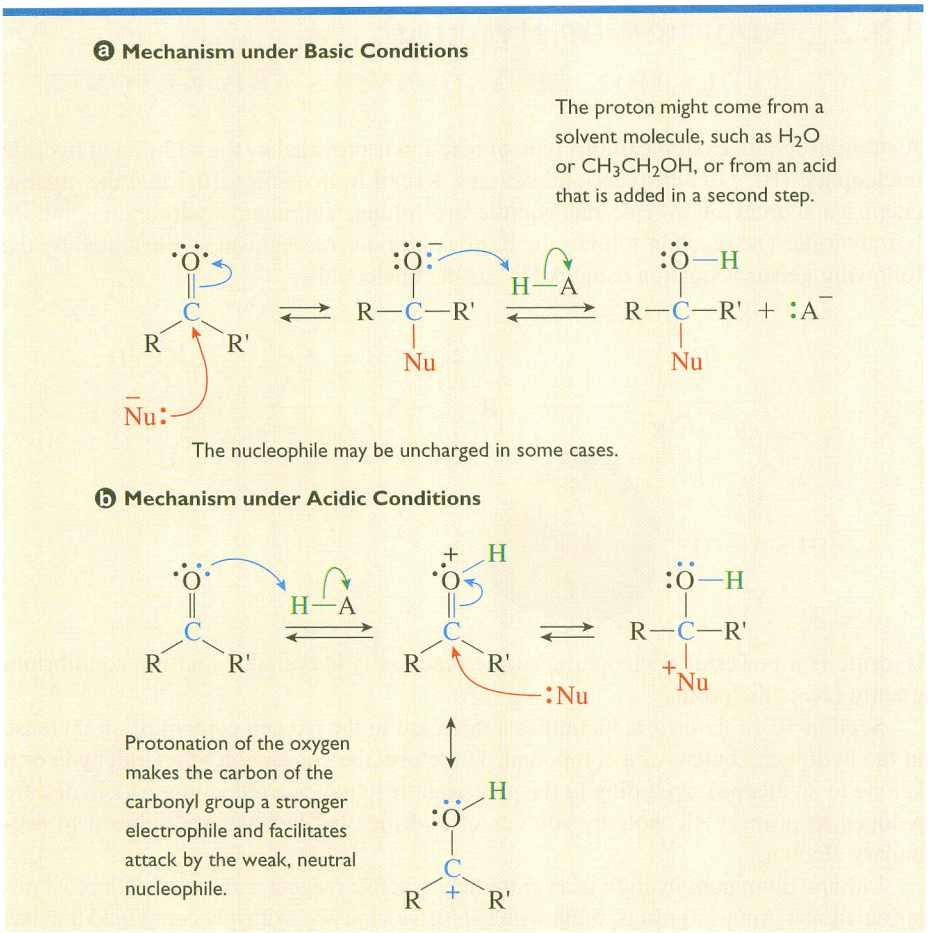


Figure 18.1

MECHANISMS OF NUCLEOPHILIC ADDITIONS TO A CARBONYL GROUP UNDER (a) BASIC AND (b) ACIDIC CONDITIONS.

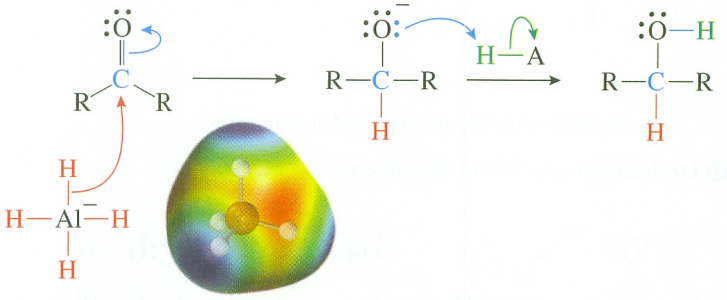
contrast, the reactions presented in Chapter 11 are called *electrophilic additions* because the electrophile adds in the slow step.

In some ways the reactions described in this chapter are simpler than those described in Chapter 11. The stereochemistry of the addition is not a concern here because there is no way to determine whether the addition occurs in a syn or an anti manner. Furthermore, the regiochemistry of these reactions is simple: the nucleophile always adds to the carbon of the carbonyl group.

The equilibrium in these reactions may favor the products or the reactants, depending on the strength of the nucleophile and the structure of the carbonyl compound. Stronger nucleophiles shift the equilibrium toward the products, and very strong nucleophiles give an irreversible reaction, that is, one that proceeds in only one direction, from the reactants to the products. The structure of the aldehyde or ketone exerts its influence through resonance, steric, and inductive effects, as usual. It is easiest to see these effects in examples, so let us proceed to examine some of the nucleophiles that can be used in these addition reactions.

18.2 Addition of Hydride; Reduction of Aldehydes and Ketones

A straightforward example of this type of reaction is provided by the addition of hydride nucleophile ($H:^-$) to aldehydes and ketones. Recall from Section 10.7 that the organic chemist's sources of hydride nucleophile are lithium aluminum hydride and sodium borohydride. The reaction follows the basic conditions mechanism as illustrated by the following general equation using AlH_4^- as the nucleophile:



Hydride is a powerful nucleophile, so the reaction is irreversible and the equilibrium greatly favors the product.

Section 10.14 defined reduction as a decrease in the oxygen content or an increase in the hydrogen content of a compound. Therefore, the conversion of an aldehyde or a ketone to an alcohol, according to the preceding reaction, is a reduction. Aldehydes are reduced to primary alcohols by sources of hydride, and ketones are reduced to secondary alcohols.

Lithium aluminum hydride is an extremely reactive reagent and reacts with most polar functional groups. It reacts, often with explosive violence, with any compound that has a relatively acidic hydrogen, such as an OH or NH, as shown in the following equation:

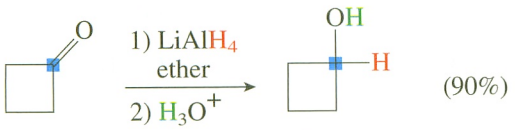
$$LiAlH_4 + 4\,ROH \longrightarrow LiAl(OR)_4 + 4\,H_2$$

Highly exothermic

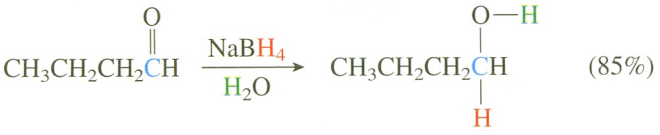
Therefore, reductions employing $LiAlH_4$ are usually conducted using ether or THF as the solvent. After addition of the hydride is complete, acid is carefully added to decompose any excess reagent and protonate the initially formed alkoxide anion. In contrast, sodium borohydride is much less reactive and reacts selectively with aldehydes and ketones in preference to many other functional groups. Its reaction with alcohols is slow enough that methanol or ethanol are often used as solvents for its reactions. The following equations provide some examples of the use of $LiAlH_4$ and $NaBH_4$ to reduce aldehydes and ketones. One mole of each of these reagents is capable of reducing four moles of carbonyl compound, although an excess of the hydride is usually employed.

$$CH_3(CH_2)_5CH \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4,\ \text{ether}} CH_3(CH_2)_5CH \quad (86\%)$$

Heptanal — 1-Heptanol

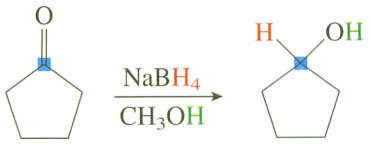


(90%)



(85%)

Butanal 1-Butanol

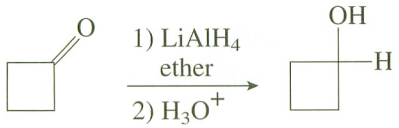


(90%)

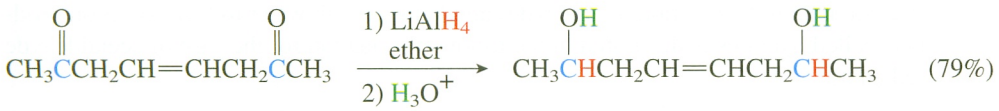
Cyclopentanone Cyclopentanol

PROBLEM 18.1

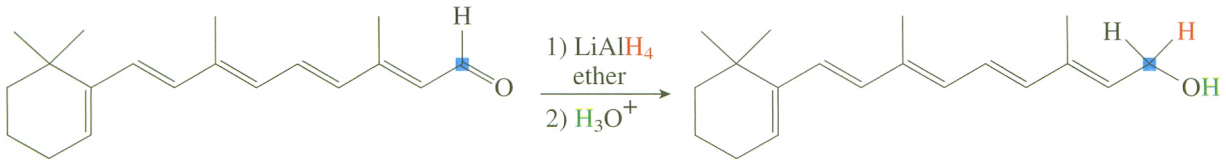
Show the steps involved in the mechanism for this reaction:



The hydride nucleophile from $LiAlH_4$ and $NaBH_4$ attacks only electrophilic carbons. Isolated carbon–carbon double bonds and the double bonds of aromatic rings do not react with these reagents. This means that carbonyl groups can be selectively reduced in the presence of CC double bonds as illustrated in the following examples. (Recall from Section 11.12 that carbon–carbon double bonds can be selectively reduced in the presence of carbonyl groups using hydrogen and a catalyst.)

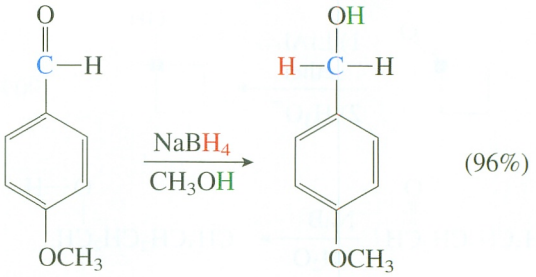


(79%)



Vitamin A aldehyde (retinal)

(75%)
Vitamin A (retinol)

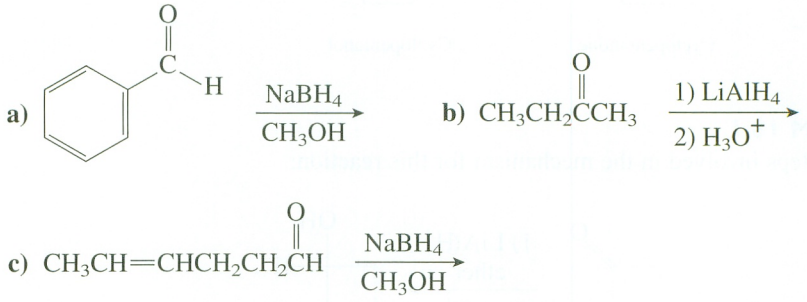


p-Methoxybenzaldehyde *p*-Methoxybenzyl alchohol

The use of lithium aluminum hydride or sodium borohydride provides the best method for the reduction of aldehydes and ketones to alcohols.

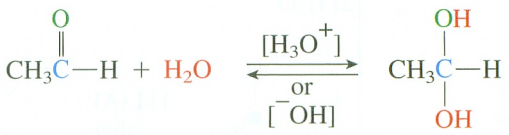
PROBLEM 18.2

Show the products of these reactions:



18.3 Addition of Water

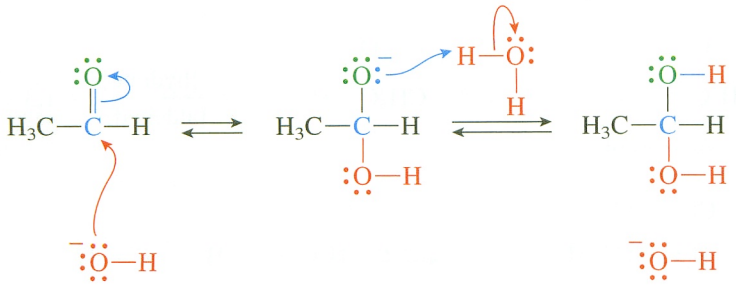
An example of the reaction of aldehydes and ketones with water to form addition products called hydrates is illustrated in the following equation for the case of acetaldehyde (ethanal):



Acetaldehyde (ethanal) A hydrate

The reaction can occur by either the acidic conditions mechanism or the basic conditions mechanism, as shown in the following equations:

Mechanism in base:



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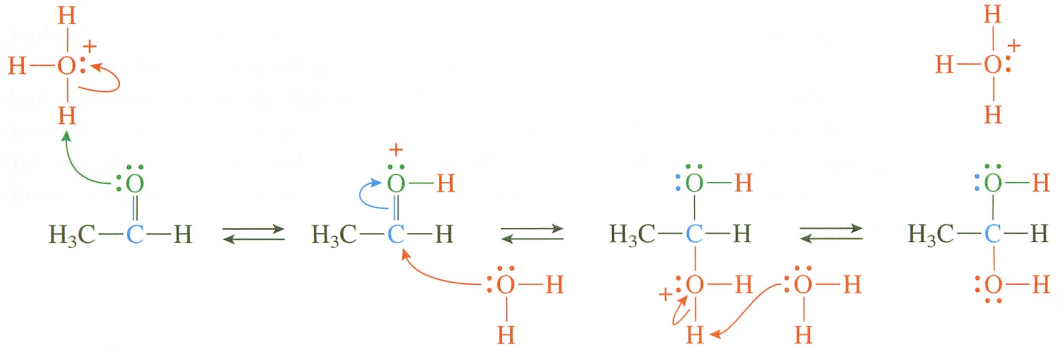
Click *Mechanisms in Motion* to view **Hydration under Base Conditions** or **Hydration under Acid Conditions.**

Mechanism in acid:



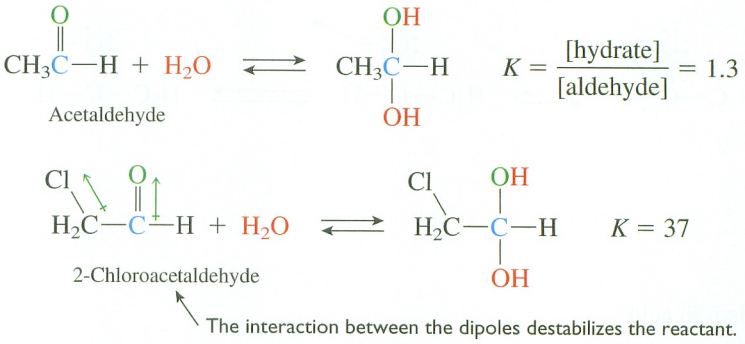
Note that in both cases the base or acid that is consumed in the first step is regenerated in the last step, so the reactions are base catalyzed or acid catalyzed.

The reaction, by either mechanism, is fast at room temperature. However, because water is a relatively weak nucleophile, the equilibrium does not favor the product in most cases. As a result, the hydrates of aldehydes and ketones usually cannot be isolated because removal of the water solvent also drives the equilibrium back to the left. Therefore, the hydration reaction is not useful in synthesis.

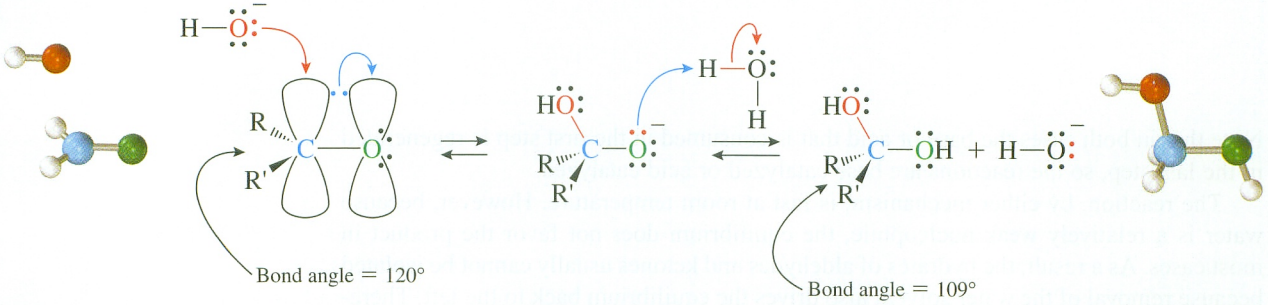
Because the equilibrium constants are neither too large nor too small, the hydration reaction provides an excellent opportunity to examine the effect of the structure of the carbonyl compound on the equilibrium constant. Let's consider inductive effects first.

The interaction of the dipole of an **electron-withdrawing group** with the large dipole of the carbonyl group destabilizes an aldehyde or ketone more than it destabilizes the hydrate product. This causes the equilibrium to shift to the right, toward the product, resulting in a larger equilibrium constant. In contrast, an **electron-donating group** stabilizes the aldehyde or ketone more than the product and causes the equilibrium to shift toward the reactants. As an illustration of these effects, let's compare the equilibrium constant for hydrate formation for acetaldehyde ($K = 1.3$) to that for 2-chloroacetaldehyde ($K = 37$). The presence of an electronegative chlorine substituent in 2-chloroacetaldehyde causes the equilibrium constant to increase substantially. (Recall that an equilibrium constant near 1 means that nearly equal amounts of reactant and product are present at equilibrium. In the case of an aqueous solution of acetaldehyde, with $K = 1.3$, the hydrate constitutes 57% of the mixture at equilibrium and the aldehyde constitutes 43%. In the case of

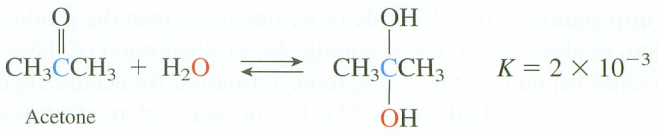
2-chloroacetaldehyde, with $K = 37$, the products are favored at equilibrium; the hydrate constitutes 97% of the mixture.)



The position of the equilibrium is also influenced by steric effects. The product, which is sp^3 hybridized and approximately tetrahedral, has the groups bonded to the hydrate carbon closer together (bond angles ~ 109°) than they are in the reactant, which is sp^2 hybridized with bond angles of ~ 120°. There is more steric hindrance between the groups in the product than there is in the reactant. Therefore, larger substituents shift the equilibrium toward the less crowded carbonyl form and decrease the equilibrium constant.



An important example of this effect is the decrease in equilibrium constants for ketones as compared to aldehydes. The replacement of the aldehyde hydrogen of acetaldehyde ($K = 1.3$) with a methyl group, to produce acetone ($K = 2 \times 10^{-3}$), results in a decrease in the equilibrium constant for hydration by a factor of approximately 1000. The inductive effect of the electron-donating alkyl group also helps shift the equilibrium for ketones toward the reactant.



In general, the equilibrium lies more toward the addition product for an aldehyde than it does for a ketone in all of the reactions in this chapter. These factors affect the rate of the reaction in the same manner, so aldehydes also react more rapidly than ke-

tones because it is easier for the nucleophile to approach the less hindered (and more electrophilic) carbonyl group of the aldehyde. (The transition state for nucleophilic attack on an aldehyde has less steric strain than the transition state for nucleophilic attack on a ketone.) Additional examples of both steric and electronic effects are provided in Table 18.1. These same electronic and steric effects also apply to the other nucleophilic additions discussed subsequently in this chapter.

PROBLEM 18.3

When acetone is treated with $H_2{}^{18}O$ (water which has some of its ^{16}O atoms replaced with ^{18}O atoms), the ^{18}O atoms are incorporated into the carbonyl group of the ketone. Show the steps in the mechanism for this reaction in the presence of acid:

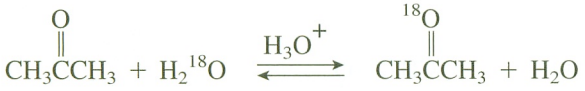
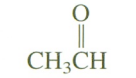
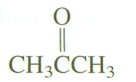
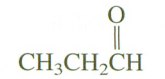
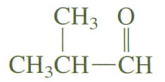
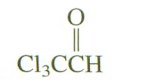
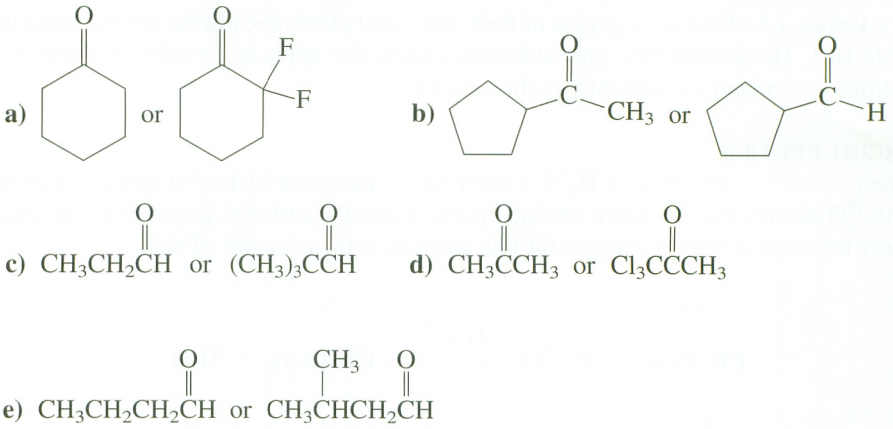


Table 18.1 Some Equilibrium Constants for Hydrate Formation

Compound	K	Comments
 Formaldehyde	2×10^3	Formaldehyde has a large equilibrium constant for hydrate formation because it has no bulky, electron-donating alkyl groups. It is more than 99.9% in the hydrated form in aqueous solution. The "formaldehyde" or formalin used to preserve biological samples is actually a concentrated solution of the hydrate in water. Formaldehyde itself is a gas.
 Acetaldehyde	1.3	The more hindered carbonyl carbon of acetaldehyde is less reactive. Acetaldehyde is slightly more than 50% hydrated in aqueous solution.
 Acetone	2×10^{-3}	Acetone, with an even more hindered carbonyl carbon, forms only a negligible amount of hydrate.
	0.71	As can be seen by comparing these two examples to acetaldehyde, an increase in steric hindrance further from the carbonyl carbon results in only a small decrease in the equilibrium constant.
	0.44	
	37	As can be seen by comparing these two examples to acetaldehyde, the inductive effect of chlorine shifts the equilibrium toward the hydrate. When three chlorines are present, the product, known as chloral hydrate, can be isolated (mp = 57°C). It is a powerful hypnotic and is the active ingredient of a "Mickey Finn," or knockout drops.
	2.8×10^4	

PROBLEM 18.4

Explain which compound has the larger equilibrium constant for hydrate formation:

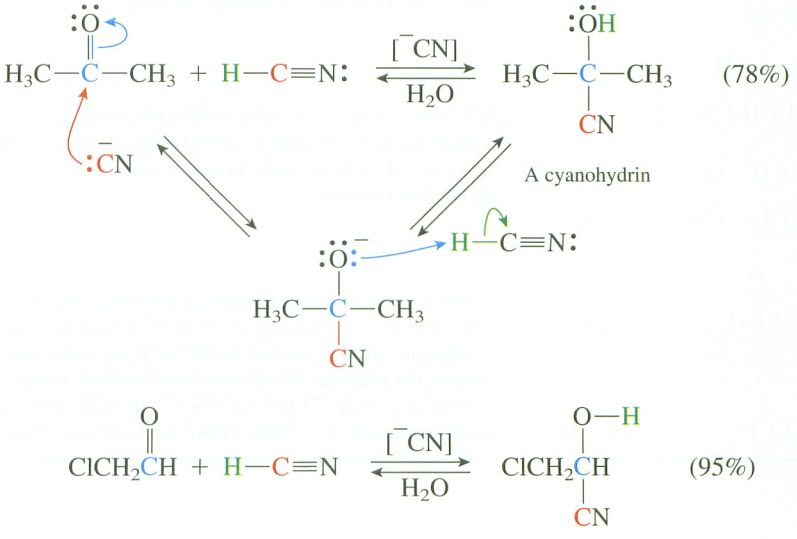


PROBLEM 18.5

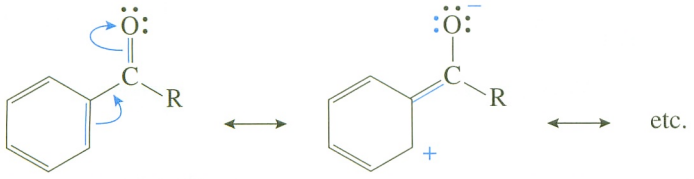
Arrange these compounds in order of increasing equilibrium constant for hydrate formation:

18.4 Addition of Hydrogen Cyanide

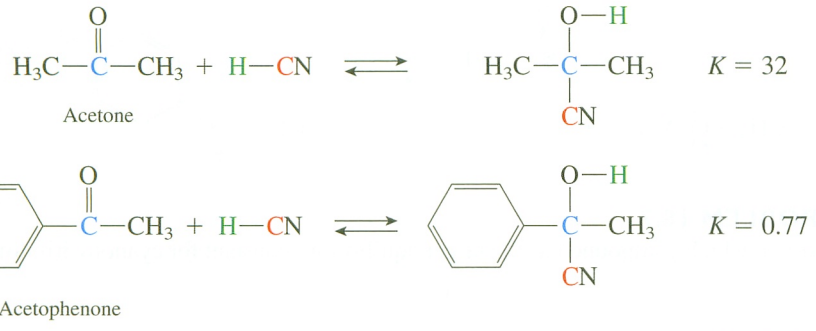
Hydrogen cyanide adds to aldehydes and ketones to form products known as cyanohydrins, as shown in the following examples. The reaction proceeds by the basic conditions mechanism and is catalyzed by cyanide ion.



The equilibrium constants are somewhat larger for cyanohydrin formation than they were for hydrate formation because cyanide ion is a stronger nucleophile than water. Therefore, aldehydes and many ketones give good yields of the addition product. However, ketones that are conjugated with benzene rings have unfavorable equilibrium constants. In such compounds the reactant has resonance stabilization due to the conjugation of the carbonyl group with the aromatic ring (see the following structures). This stabilization is lost in the product, resulting in the product being less favored at equilibrium.



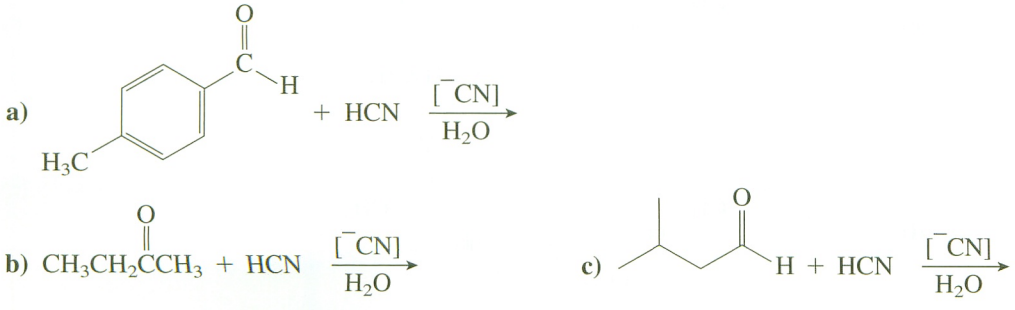
As an example of this effect, the equilibrium constant for the reaction of acetone with hydrogen cyanide is 32, whereas the equilibrium constant for a similar reaction of acetophenone is 0.77:



Under typical conditions the reaction of acetone with hydrogen cyanide ($K = 32$) has most of the reactants converted to the product at equilibrium. This allows the cyanohydrin to be obtained in acceptable isolated yield (78%). In contrast, the amount of cyanohydrin product that is present at equilibrium in the reaction of acetophenone ($K = 0.77$) is too low for the reaction to be synthetically useful unless some method is used to drive the equilibrium toward the product.

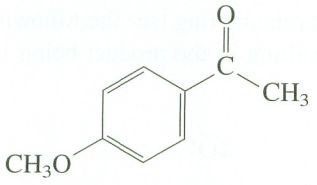
PROBLEM 18.6

Show the products of these reactions:

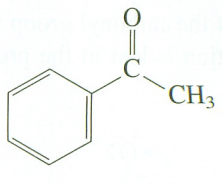


PRACTICE PROBLEM 18.1

Explain why *p*-methoxyacetophenone has a smaller equilibrium constant for cyanohydrin formation than does acetophenone.



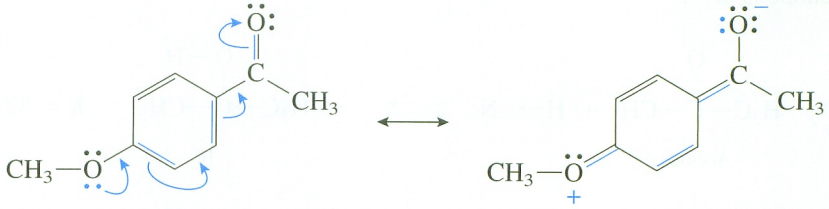
p-Methoxyacetophenone



Acetophenone

Solution

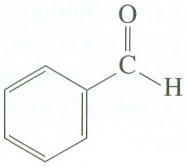
The methoxy group donates electrons to the carbonyl carbon by resonance, making it less electrophilic and less reactive. Therefore, the equilibrium constant for cyanohydrin formation is larger for acetophenone than for *p*-methoxyacetophenone.

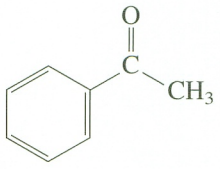
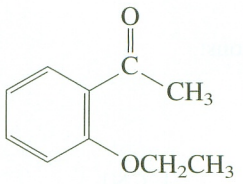


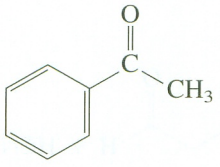
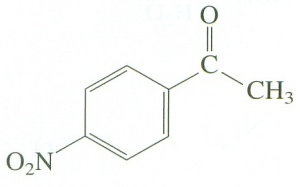
PROBLEM 18.7

Explain which compound has the larger equilibrium constant for cyanohydrin formation:

a) $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_3$ or $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$

b) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$ or 

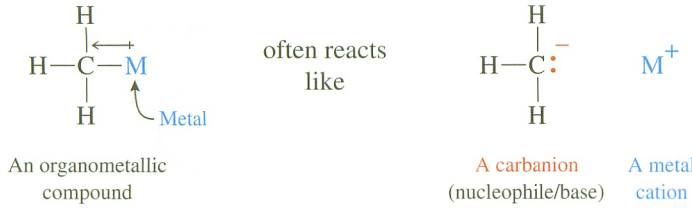
c)  or 

d)  or 

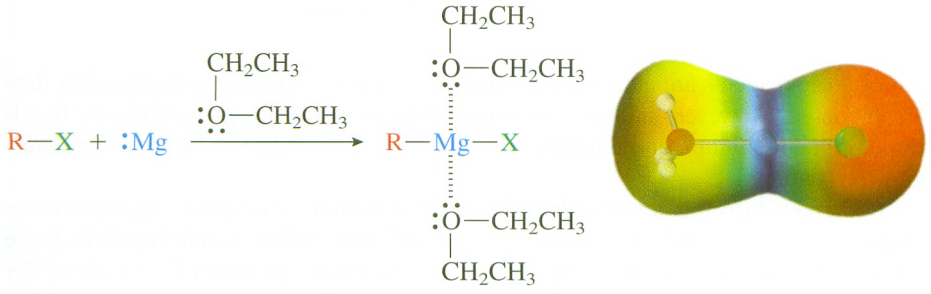
18.5 Preparation and Properties of Organometallic Nucleophiles

Carbon nucleophiles are very useful species because their reactions with carbon electrophiles result in the formation of carbon–carbon bonds. Section 10.8 introduced acetylide anions as nucleophiles that could be used in S_N2 reactions. These nucleophiles are prepared by reacting 1-alkynes with a strong base such as sodium amide. The relatively acidic hydrogen on the *sp*-hybridized carbon is removed in this acid–base reaction:

Hydrogens bonded to sp^3- and sp^2-hybridized carbons are not acidic enough to be removed by bases that are commonly available in the laboratory. However, the carbon–halogen bond of many organic halides can be converted to a carbon–metal bond, resulting in the formation of an **organometallic compound.** Because the metal is less electronegative than carbon, the bond is polarized in the direction opposite to that found in most organic compounds; that is, the negative end of the dipole is on the carbon and the positive end is on the metal. Although the carbon–metal bond is covalent, many organometallic compounds react as though they are carbanions and are useful as carbon nucleophiles.

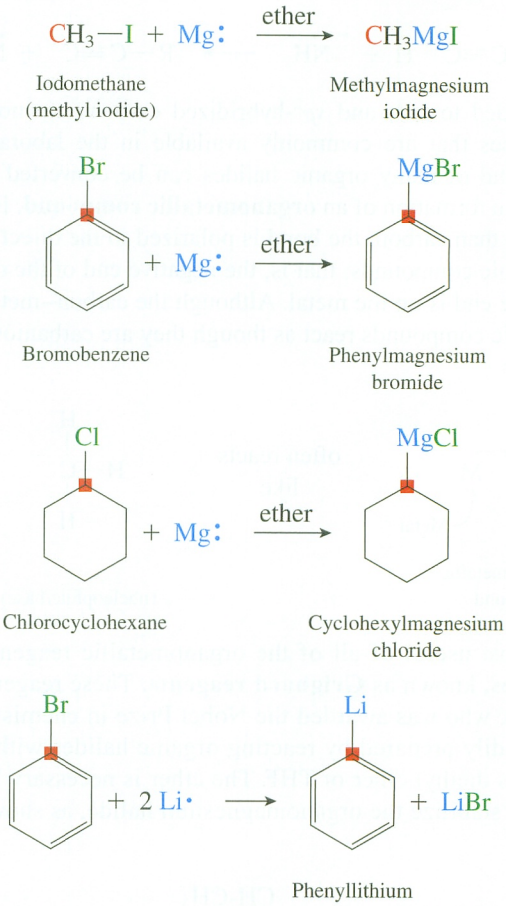


Perhaps the most useful of all of the organometallic reagents are the **organomagnesium halides,** known as **Grignard reagents.** These reagents were developed by Victor Grignard, who was awarded the Nobel Prize in chemistry in 1912 for this work. They are readily prepared by reacting organic halides with magnesium metal in a solvent such as diethyl ether or THF. The ether is necessary because it acts as a Lewis base to help stabilize the organomagnesium halide, as shown in the following equation:



The structure of the R group of RX can vary widely as long as no other reactive functional group is present. The halogen of RX can be iodine (most reactive), bromine, or chlorine (least reactive); fluorine is not commonly used. Several examples are provided

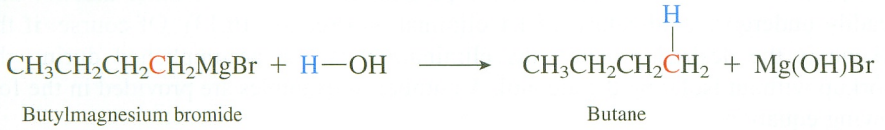
in the following equations. (To simplify writing these reactions, the ether molecules coordinated to the magnesium are not shown.) In similar fashion, organolithium reagents can be prepared by reactions of lithium metal with organic halides. Their reactions are nearly identical to those of the Grignard reagents, although the organolithium reagents are slightly more reactive. Note that magnesium, which has two electrons in its valence shell, forms two bonds (not counting its bonds with the ether molecules), whereas lithium, with a single electron in its valence shell, forms only one bond. Therefore, 2 moles of lithium are needed for this reaction.



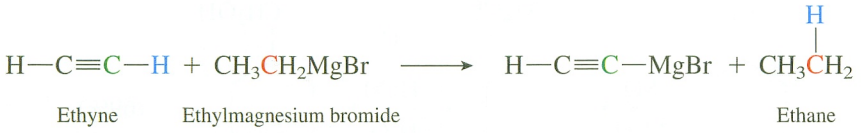
All of these reagents are quite reactive and are commonly used immediately after they are prepared. However, solutions of some of them, including methyllithium, butyllithium, phenyllithium, and a number of simple Grignard reagents, are now commercially available.

Let's now turn our attention to the chemical behavior of these organometallic reagents. As mentioned previously, even though the carbon–metal bonds in these compounds are predominantly covalent, they often react as would be predicted for the corresponding carbanion, although the identity of the metal certainly modifies their behavior somewhat. As expected for carbanions whose pK_a's would be in the

range of 45 to 50, all of these organometallic reagents behave as strong bases and react rapidly with even fairly weak acids, such as water and alcohols, as illustrated in the following equation. Therefore, the solvents that are used for their preparation must be scrupulously dried, and compounds containing OH or NH groups must be avoided.

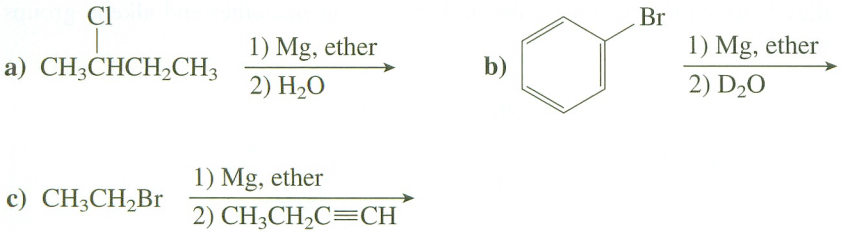


Even a 1-alkyne is acidic enough to react with a Grignard reagent. This reaction is the most common method of preparing Grignard reagents derived from these alkynes:



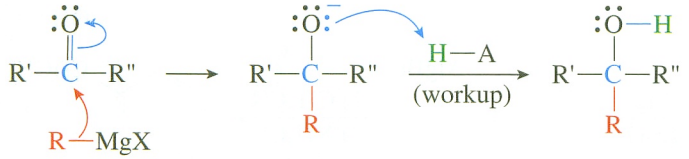
PROBLEM 18.8

Show the products of these reactions:



18.6 Addition of Organometallic Nucleophiles

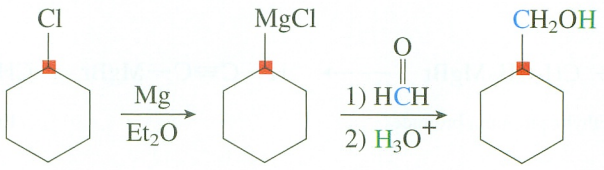
The reaction of Grignard reagents and organolithium compounds with aldehydes and ketones is perhaps the most useful method for the preparation of alcohols. The reaction is conducted under basic conditions and proceeds according to the following general mechanism:



Because these organometallic reagents are powerful nucleophiles, the reaction is irreversible. After the addition is complete, acid is added in the workup step to pro-

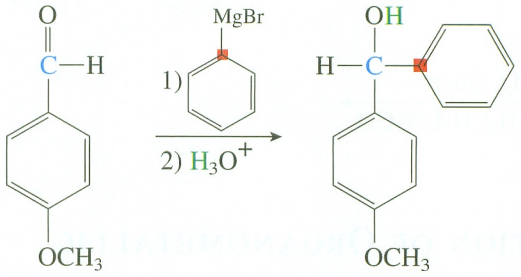
tonate the alkoxide ion and produce the alcohol. Reactions employing formaldehyde as the carbonyl component produce primary alcohols, those using other aldehydes produce secondary alcohols, and those using ketones produce tertiary alcohols. Solutions of hydrochloric or sulfuric acid are commonly used in the protonation step. However, to avoid alkene formation, the weaker acid, ammonium chloride ($pK_a = 9$) in aqueous solution, is used when the product is a tertiary or other alcohol that readily undergoes acid-catalyzed E1 elimination (Section 10.13). Of course, if the alkene is the desired product, the elimination can be accomplished during the workup without isolating the alcohol. A number of examples are provided in the following equations.

The reaction of an organometallic reagent with formaldehyde produces a primary alcohol:



(69%)

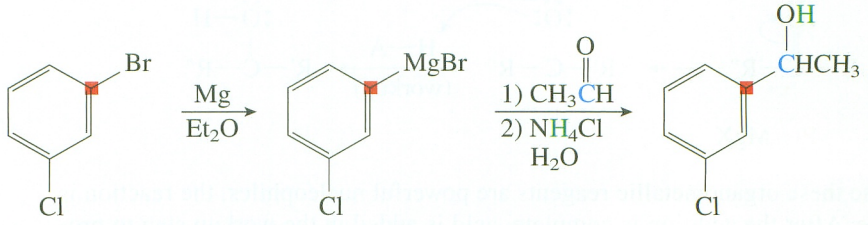
Reactions with other aldehydes produce secondary alcohols. Although the presence of most other functional groups (OH, NH, carbonyl groups, and so on) must be avoided because they react with Grignard or organolithium reagents, ether and alkene groups can be present:



(90%)

p-Methoxybenzaldehyde

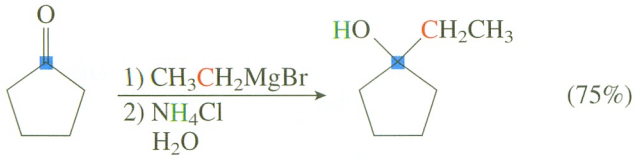
In the next example the bromine, being more reactive than chlorine, selectively reacts to form the Grignard reagent. The product alcohol is especially prone to E1 elimination (the carbocation would be stabilized by resonance), so the weak acid, ammonium chloride, is used in the workup step.



(88%)

m-Bromochlorobenzene

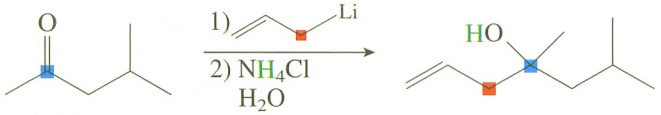
Reactions with ketones give tertiary alcohols. These are very prone to E1 elimination, so weak acid is used in the workup.



(75%)

Cyclopentanone

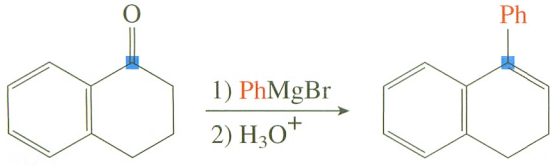
Organolithium reagents work well in any of these reactions:



(72%)

4-Methyl-2-pentanone

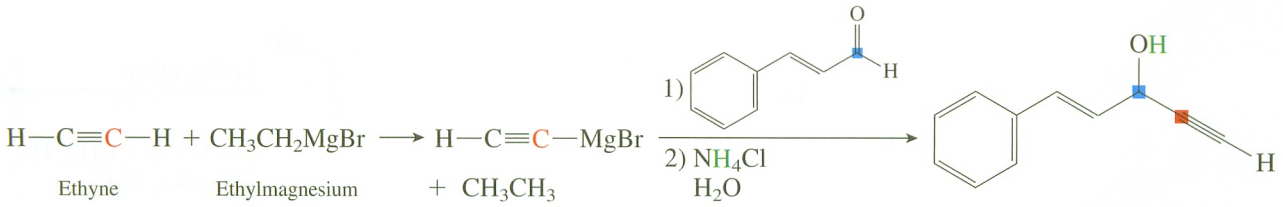
If the product resulting from elimination of water from the alcohol is desired, then the workup can be conducted by using a stronger acid so that the reaction proceeds directly to the alkene without the isolation of the alcohol.



(48%)

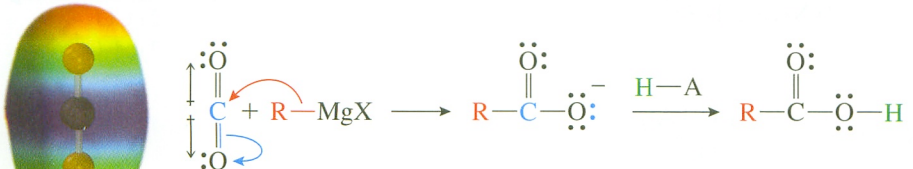
α-Tetralone

Acetylenic Grignard reagents are commonly prepared by reaction of the appropriate 1-alkyne with an alkyl Grignard reagent, such as ethylmagnesium bromide.



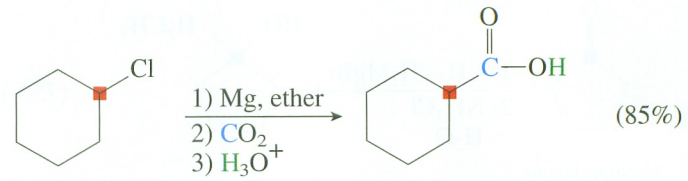
(69%)

The carbon of carbon dioxide is electrophilic, similar to a carbonyl carbon. Grignard reagents react with carbon dioxide to form salts of carboxylic acids:



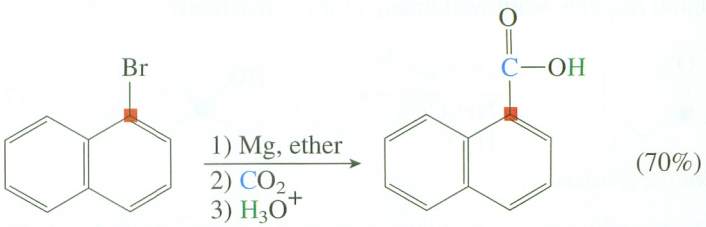
Carbon dioxide

Acidification of the reaction mixture produces a carboxylic acid. Examples are provided in the following equations:



(85%)

Chlorocyclohexane

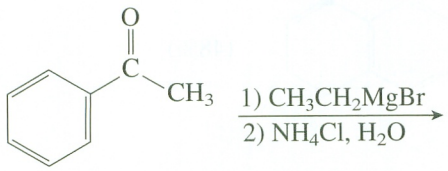


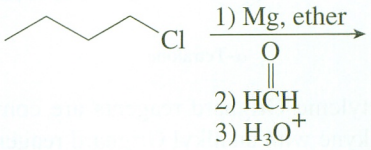
(70%)

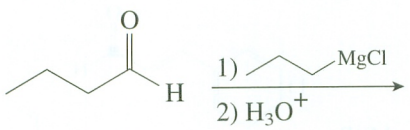
1-Bromonaphthalene

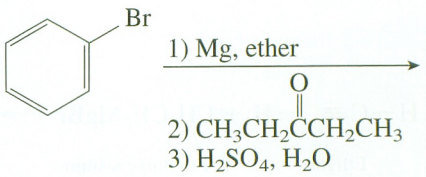
PROBLEM 18.9

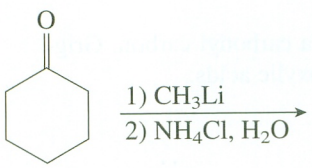
Show the products of these reactions:

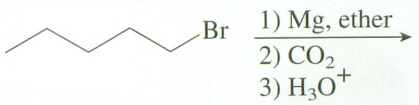
a) 

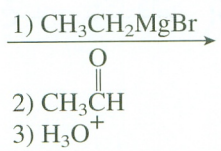
b) 

c) 

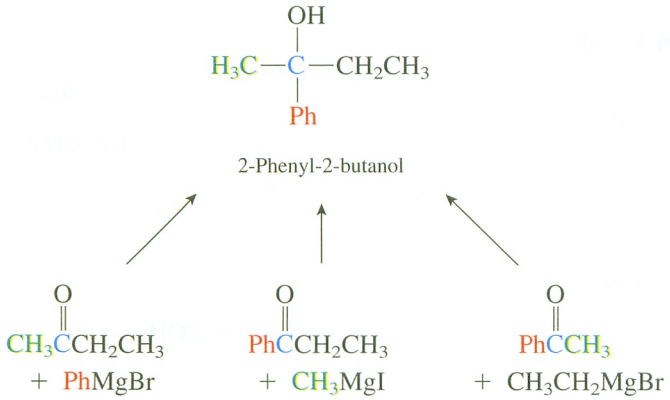
d) 

e) 

f) 

g) $CH_3C{\equiv}CH$ 

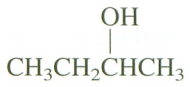
The Grignard reaction is an important and versatile way to prepare alcohols. Whenever an alcohol is encountered as a synthetic target, this reaction should be considered because it forms a carbon–carbon bond, building the alcohol from smaller compounds, and it often allows more than one route to the desired product. For example, suppose the target is 2-phenyl-2-butanol. This alcohol can be prepared by three different Grignard reactions:



Because the product is a tertiary alcohol, each of these reactions must be acidified with a weak acid (NH_4Cl/H_2O) to avoid elimination. Which of these pathways is the best depends on a number of factors, such as the availability of the ketone and the halide needed to prepare the Grignard reagent and the yield of the reaction.

PRACTICE PROBLEM 18.2

Show two ways to prepare 2-butanol using Grignard reagents.



2-Butanol

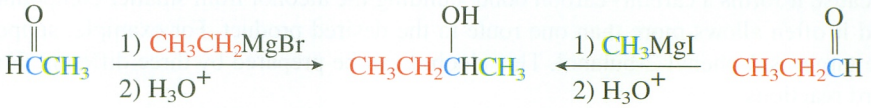
Strategy

When you encounter an alcohol as a synthetic target, consider using a Grignard reaction to synthesize it. The carbon bonded to the hydroxy group was the electrophilic carbon of the carbonyl group of the reactant. One of the alkyl groups bonded to this carbon was the nucleophilic carbon of the Grignard reagent or alkyllithium reagent. There are often several ways to accomplish the synthesis, depending on which alkyl group is added as the nucleophile. Remember to work up the reaction with the weak acid NH_4Cl if the product alcohol is prone to E1 elimination.

Solution

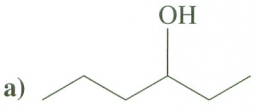
The carbon (blue) bonded to the hydroxy group in the alcohol comes from the carbonyl carbon electrophile of the starting material. This carbon is also bonded to a methyl group and an ethyl group. We can add the ethyl group, using the reaction of ethylmag-

nesium bromide and ethanal, or we can add the methyl group, using methylmagnesium iodide and propanal.

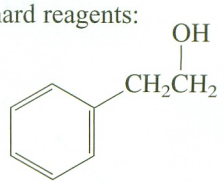


PROBLEM 18.10

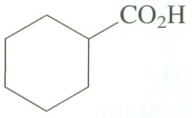
Suggest syntheses of these compounds using Grignard reagents:



a) (2 ways)

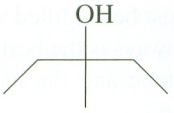


b)

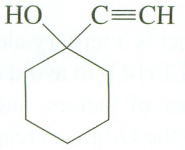


c)

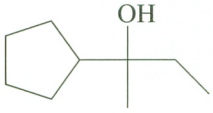
d) Ph_3COH



e) (2 ways)



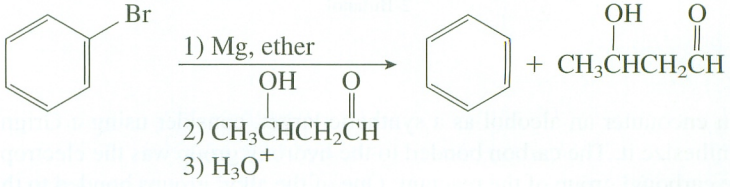
f)



g) (3 ways)

PROBLEM 18.11

When the Grignard reaction shown in this equation is attempted, the products are benzene and the starting hydroxyaldehyde. Explain this result.

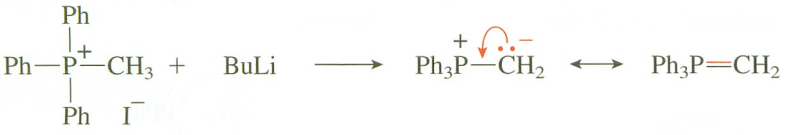


18.7 Addition of Phosphorus Ylides; The Wittig Reaction

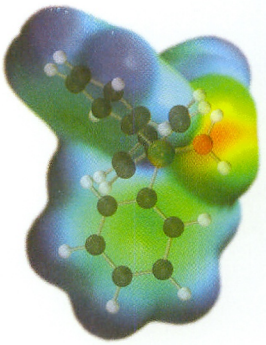
In Chapters 9 and 10 the use of elimination reactions to prepare alkenes was described. The major problem with that method is that a mixture of alkenes is often produced, resulting in lower yields and separation problems. The Wittig reaction provides an alter-

native method for the synthesis of alkenes. It is especially useful because it results in carbon–carbon bond formation and the position of the double bond is completely controlled. Georg Wittig shared the 1979 Nobel Prize in chemistry for developing this reaction. (He shared the award with H. C. Brown, who developed the hydroboration reaction; see Section 11.7.)

The nucleophile used in this reaction is called an **ylide.** It is a carbanion that is bonded to a positive phosphorus group that helps to stabilize it:



Phosphonium salt — Butyllithium — Ylide — Minor contributor

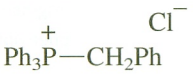


Electrostatic potential map of $Ph_3\overset{+}{P}—\ddot{\overset{-}{C}}H_2$

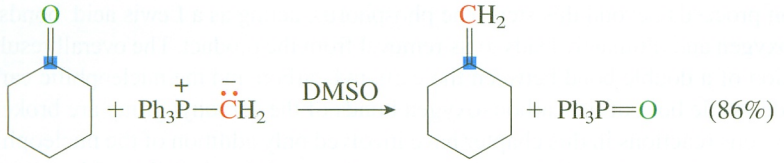
The ylide is prepared by deprotonating a triphenylalkylphosphonium salt with a strong base, commonly an organometallic base such as butyllithium or phenyllithium. The hydrogens on the carbon that is bonded to the phosphorus of the salt are somewhat acidic because the carbanion of the conjugate base (the ylide) is stabilized by the inductive effect of the positive phosphorus atom. In addition, a resonance structure with five bonds to phosphorus makes a minor contribution to the structure and provides some additional stabilization. The triphenylalkylphosphonium salt can be prepared by an S_N2 reaction of triphenylphosphine with the appropriate alkyl halide (see Section 10.9).

PROBLEM 18.12

Show a preparation of this phosphonium salt from an alkyl halide:

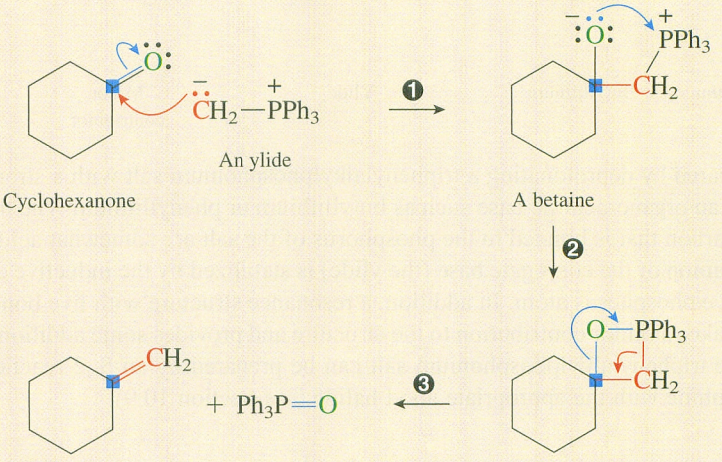


The reaction of the ylide with an aldehyde or ketone results in the formation of an alkene with the double bond connecting the carbonyl carbon of the reactant to the anionic carbon of the ylide, as shown in the following example:



The by-product is triphenylphosphine oxide. The ylide is a strong nucleophile, so the equilibrium greatly favors the products and the reaction is irreversible.

The mechanism for this reaction is shown in Figure 18.2. The first part of the mechanism is similar to the others that have been presented so far: the nucleophile (the negative carbon of the ylide) attacks the carbonyl carbon. However, unlike the previous cases, this



❶ This reaction begins in the same manner as other reactions that proceed by the mechanism for basic conditions. The nucleophile, the negative carbon of the ylide, attacks the carbonyl carbon.

However, the reaction does not stop at this intermediate, known as a **betaine.**

❷ Rather, the oxygen forms a bond to the phosphorus in a Lewis acid–base reaction, forming a four-membered ring. (The mechanism for this reaction is still being investigated, and it may be that these first two steps occur in a concerted manner.)

The reaction proceeds directly to the alkene. The intermediate betaine and oxaphosphetane are not isolated.

The resulting four-membered ring, containing ing an oxygen and a phosphorus, is called an **oxaphosphetane.**

❸ Under the reaction conditions it spontaneously fragments to give the product alkene and triphenylphosphine oxide.

Active Figure 18.2 ORGANIC Chemistry Now™

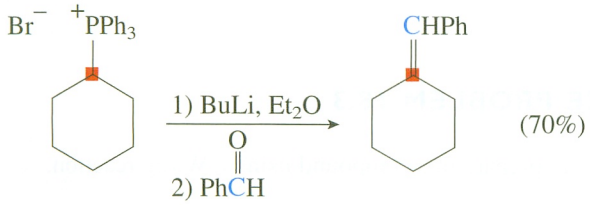
MECHANISM OF THE WITTIG REACTION. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

reaction proceeds beyond this step. The phosphorus, acting as a Lewis acid, bonds to the basic oxygen and ultimately leads to its removal from the product. The overall result is the formation of a double bond between the carbonyl carbon and the nucleophilic carbon of the ylide, while both of the carbon–oxygen bonds of the carbonyl group are broken.

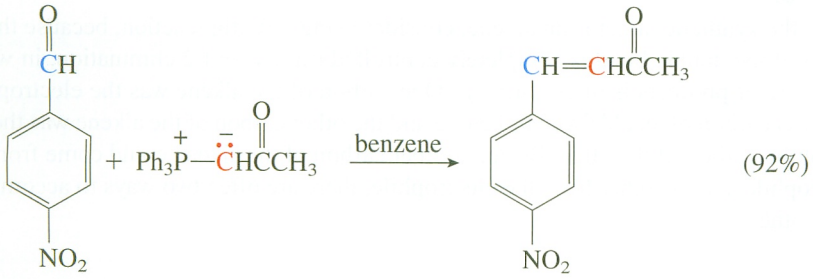
Previous reactions in this chapter have involved only addition of the nucleophile and a hydrogen to the carbonyl group. In this reaction, addition is followed by elimination of the oxygen to form a double bond between the carbonyl carbon and the nucleophile. Such an **addition–elimination** reaction occurs when the nucleophile has or can generate (by the loss of a proton or a phosphorus group) a second pair of electrons that can be used to form a second bond to the electrophilic carbon. In the case of the Wittig reaction, the phosphorus and the oxygen are eliminated to form the alkene. The forma-

tion of the strong phosphorus–oxygen bond helps make this step of the reaction favorable. (Note that the previous reactions in this chapter, employing hydride, cyanide, and organometallic nucleophiles, did not have any way to form a second bond between the nucleophile and the electrophilic carbon, so only addition occurred.)

Because the location of the double bond in the product is well defined, the Wittig reaction provides probably the most useful general method for the preparation of alkenes. Some examples are provided in the following equations:

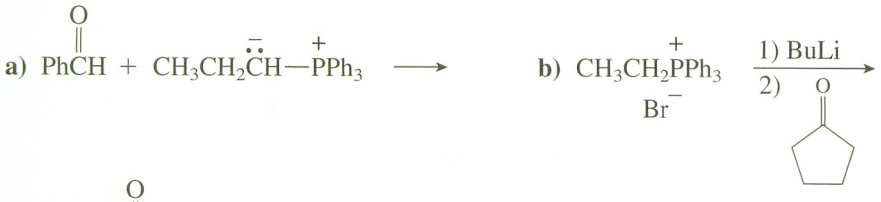


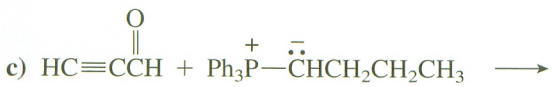
Because the electron pair of the carbanion of the ylide in the following example is stabilized by resonance delocalization with the carbonyl group, it is a weaker nucleophile. Such ylides react readily with aldehydes but do not react well with ketones.

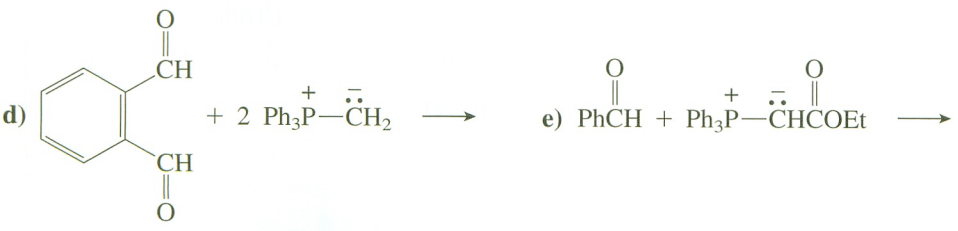


PROBLEM 18.13

Show the products of these reactions:







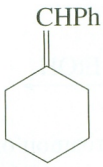
ORGANIC Chemistry Now™
Click *Coached Tutorial Problems* to practice **Grignard Reactions and Wittig Reactions.**

PROBLEM 18.14

Explain why the phosphonium salt shown in the following equation can be deprotonated by using sodium ethoxide, a much weaker base than the butyllithium that is usually needed to deprotonate other phosphonium salts.

PRACTICE PROBLEM 18.3

Show two ways to prepare this compound using a Wittig reaction.

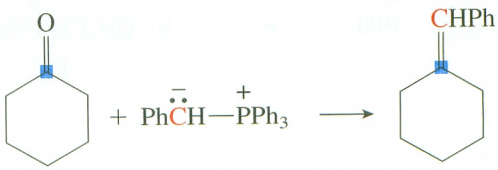


Strategy

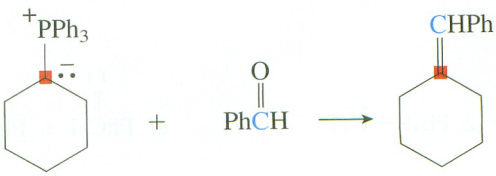
When the synthetic target is an alkene, consider using a Wittig reaction, because the location of the double bond is completely controlled (unlike an E2 elimination, in which a mixture of products is often formed). One carbon of the alkene was the electrophilic carbonyl carbon of an aldehyde or ketone and the other carbon of the alkene was the nucleophilic carbon of the ylide. Because either carbon of the alkene could come from the nucleophile and the other from the electrophile, there are often two ways to accomplish the synthesis.

Solution

Break the double bond, making one carbon the nucleophile of an ylide and the other carbon part of a carbonyl group. The two possible ways to do this in this case are as follows:



or

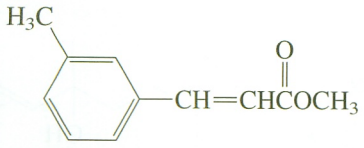


PROBLEM 18.15

Suggest syntheses of these compounds using the Wittig reaction:

a) $PhCH_2CH{=}CHCH_2CH_3$ (2 ways) **b)** $CH_3CH_2CH{=}CHCCH_2CH_3$ (O above CHC)

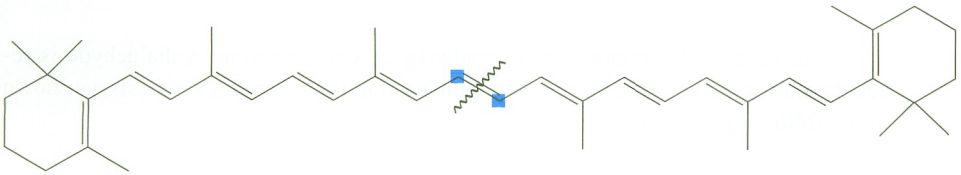
c)



Focus On

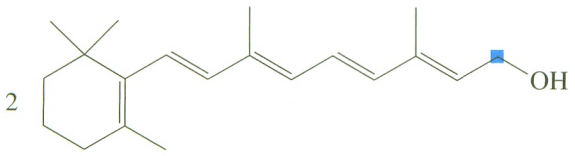
Synthesis of Vitamin A

Vitamin A, also known as retinol, is essential for vision in mammals (see the Focus On box on page 773) and is involved in a number of other important biological functions, such as bone growth and embryonic development. A deficiency in vitamin A leads to night blindness, in which the eye cannot see in dim light. Our bodies are capable of converting compounds such as β-carotene, an orange pigment that is present in many vegetables, to vitamin A. As its structure suggests, vitamin A is relatively nonpolar and therefore is not very soluble in water. It accumulates in fat deposits and is not readily excreted. For this reason, too much vitamin A is toxic.



β-Carotene

Oxidative cleavage



Vitamin A (retinol)

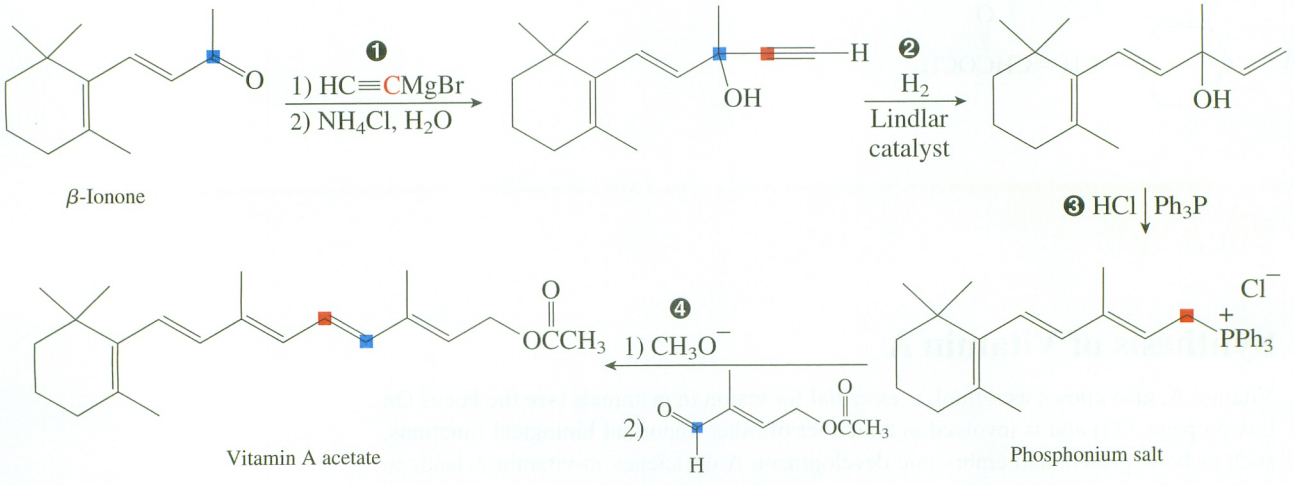
The Wittig reaction has proved to be especially useful in the synthesis of natural products, such as vitamin A, which contain a number of carbon–carbon double bonds. An industrial synthesis of vitamin A is outlined in the following equations:

Continued

❶ β-Ionone can be isolated from natural sources or synthesized in the laboratory. It is reacted with ethynyl magnesium bromide, or some other source of the anion derived from ethyne, to produce an alcohol (see Section 18.6).

❷ The triple bond is reduced to a double bond using hydrogen and the Lindlar catalyst (see Section 11.12).

❸ Then, reaction of the alcohol with triphenylphosphine under acidic conditions produces the phosphonium salt by an S_N1 reaction. A resonance-stabilized carbocation is formed and reacts at the terminal position of the chain.



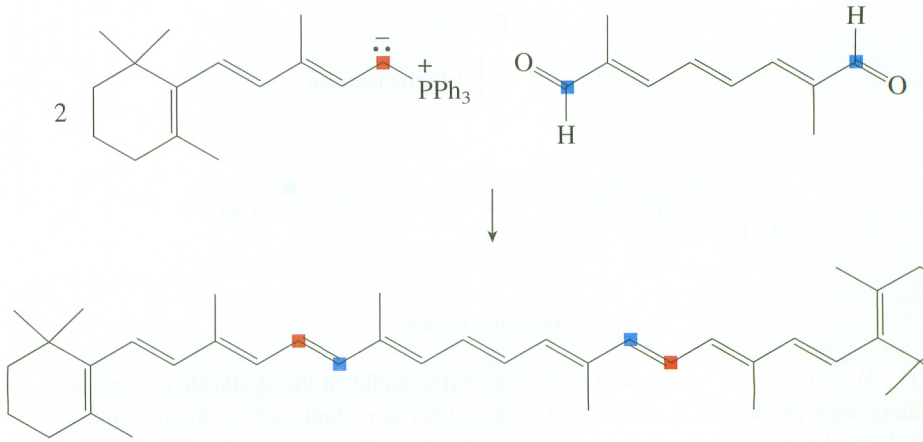
β-Ionone

Vitamin A acetate

Phosphonium salt

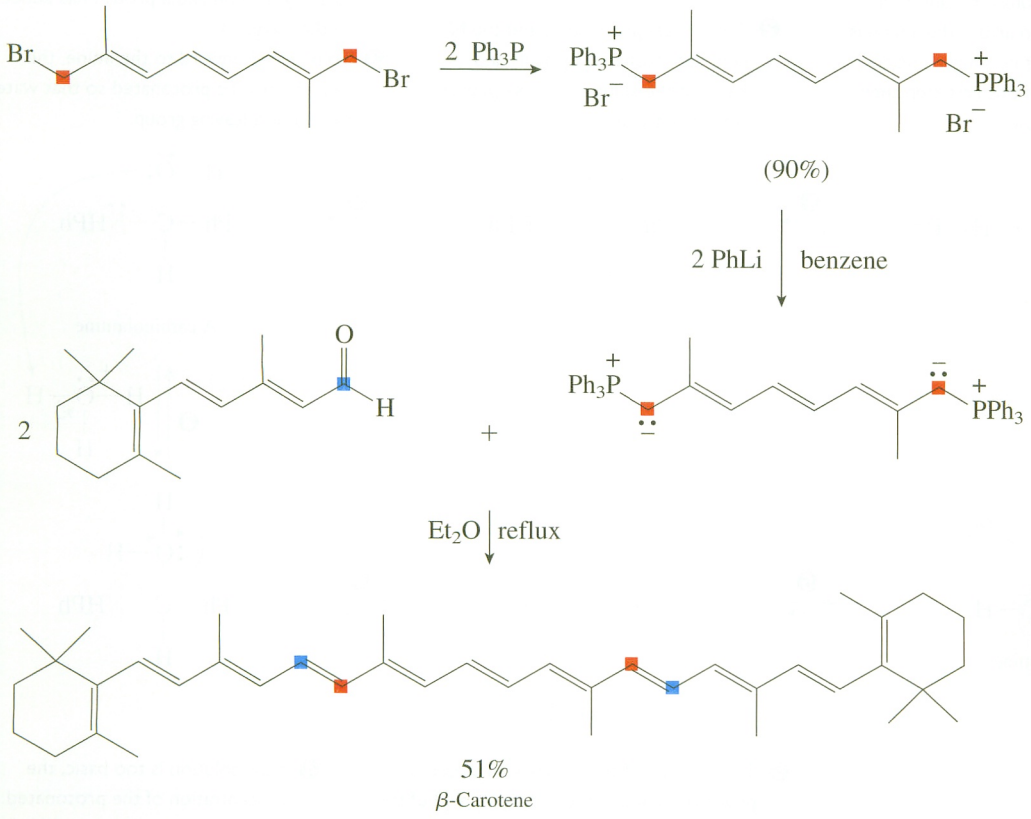
❹ The phosphonium salt is more acidic than usual because its conjugate base, the ylide, is stabilized by resonance involving the double bonds. Therefore, methoxide ion, a weaker base than usual, can be used to form the ylide. Reaction of the ylide with the aldehyde that has its hydroxy group protected as an ester produces vitamin A acetate. The acetate group can readily be removed to complete the synthesis of vitamin A (see Section 10.2).

β-Carotene is also prepared industrially by a Wittig reaction. A dialdehyde is reacted with two equivalents of the same ylide used in the vitamin A synthesis, as shown in the following equation:



β-Carotene

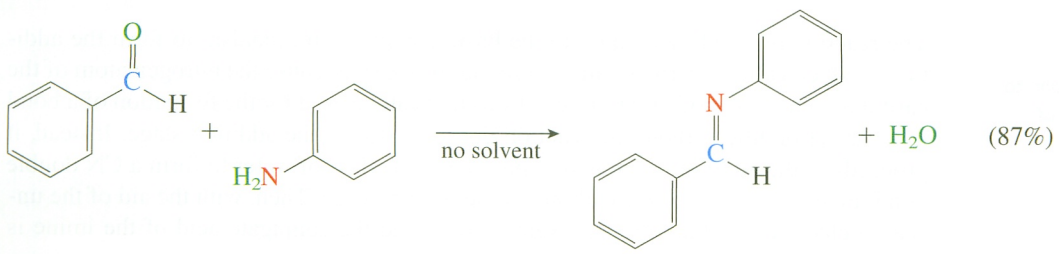
It is interesting to note that an alkene can be prepared by two different Wittig pathways, depending on which of the doubly bonded carbons was originally the carbon of the carbonyl group and which was the carbon of the ylide. Thus, the synthesis of β-carotene has also been accomplished by using the reaction of a diylide with two equivalents of an aldehyde, as illustrated in the following equations:



51%
β-Carotene

18.8 Addition of Nitrogen Nucleophiles

Amines add to the carbonyl groups of aldehydes or ketones to produce compounds containing CN double bonds and water. These nitrogen analogs of aldehydes and ketones are called **imines.**



Benzaldehyde Aniline An imine

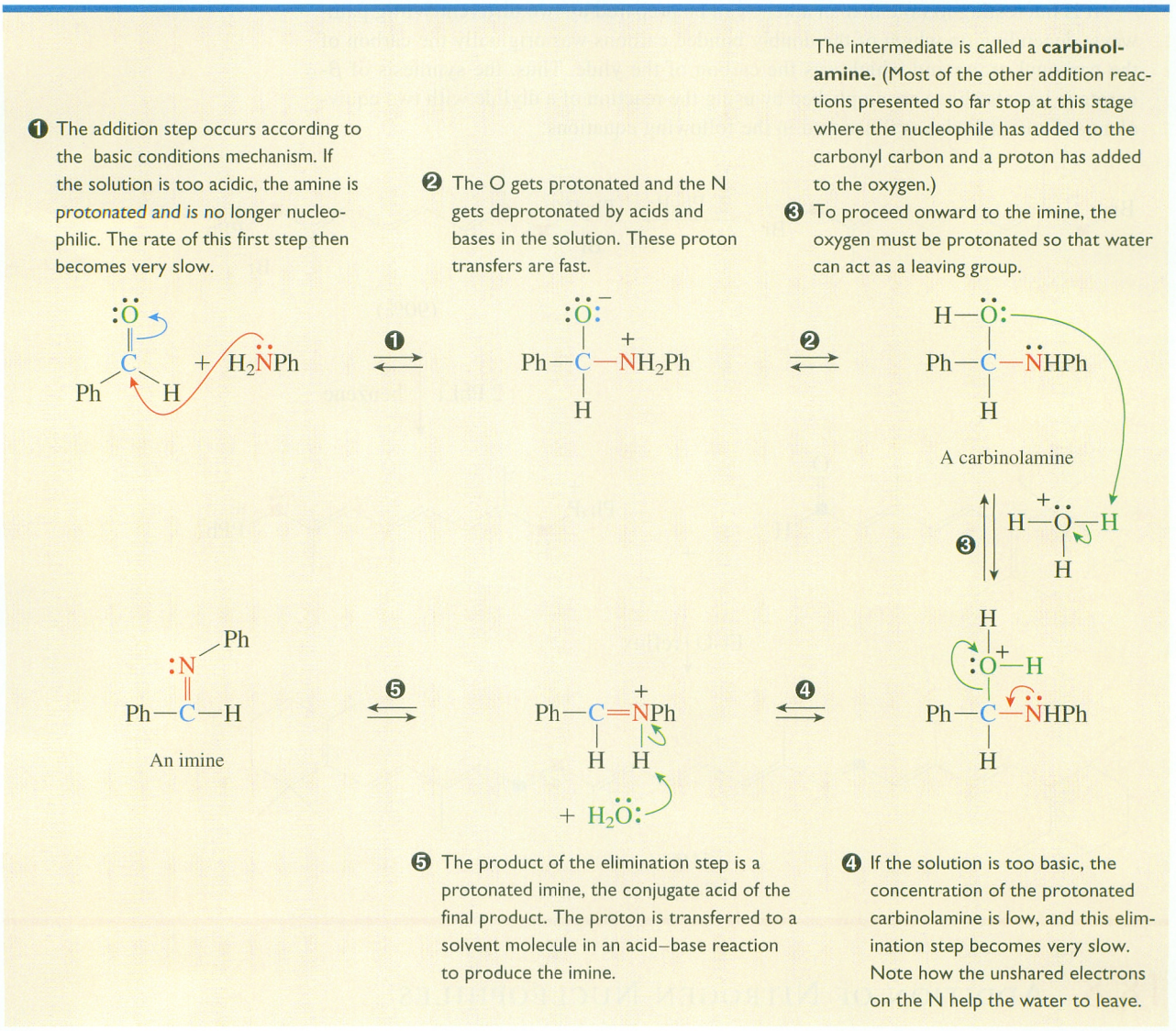


Figure 18.3

MECHANISM OF THE ADDITION OF AN AMINE TO AN ALDEHYDE TO FORM AN IMINE.

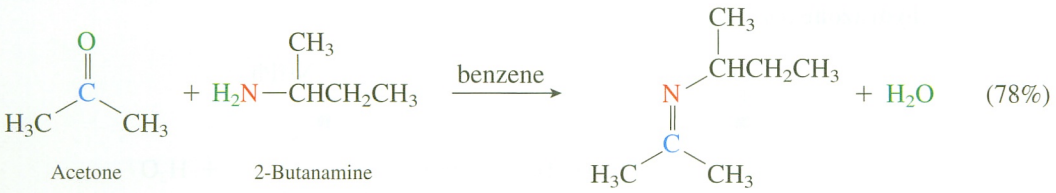
ORGANIC Chemistry Now™
Click *Mechanisms in Motion* to view the **Mechanisms of Imine Formation.**

The reaction proceeds according to the basic conditions mechanism to form the addition product, called a carbinolamine (see Figure 18.3). Because the nitrogen atom of the carbinolamine has another pair of electrons that can be used for the formation of a bond to the electrophilic carbon, the reaction does not stop at the addition stage. Instead, it proceeds to the addition–elimination product by the loss of water to form a CN double bond. First the oxygen of the carbinolamine is protonated. Then, with the aid of the unshared electrons on the nitrogen, water leaves, and the conjugate acid of the imine is formed. Loss of a proton gives the imine.

The rate of this reaction has an interesting dependence on the pH of the solution. At low pH the reaction is slow because the amine nucleophile is protonated in the strongly

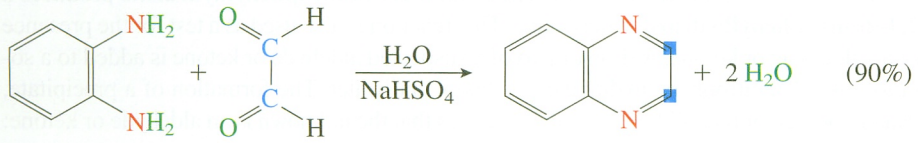
acidic solution. The low concentration of the nucleophile makes the addition step slow. At higher pH the concentration of the unprotonated amine is larger, and therefore the reaction is faster. However, if the solution is too basic, then the reaction is again slow because the concentration of the protonated carbinolamine is low, and therefore the elimination of water is slow. The maximum reaction rate occurs in the pH range of 4 to 6.

Because a CO double bond is considerably stronger than a CN double bond, the equilibrium in these reactions often favors the carbonyl compound rather than the imine. In such cases it is necessary to drive the equilibrium to the product. This is usually accomplished by removing the water as it is formed. Some additional examples of imine formation are provided in the following equations:



Acetone 2-Butanamine

The product in the following reaction results from the formation of two CN double bonds. In this case the equilibrium favors the product because of the additional resonance stabilization provided by the new aromatic ring.



In the days before the advent of spectroscopic techniques, reactions that form CN double bonds were often used in determining the structure of unidentified aldehydes and ketones. After the functional group of an unknown compound was determined and its possible identity was narrowed to a few choices, the final step in the structure determination was often the conversion of the unknown to a solid derivative using a standard chemical reaction of that functional group. The melting point of the derivative was then compared with the melting points that had been reported in the literature for the derivatives of the possible candidates. A match between the melting points was considered strong evidence in establishing the identity of the unknown.

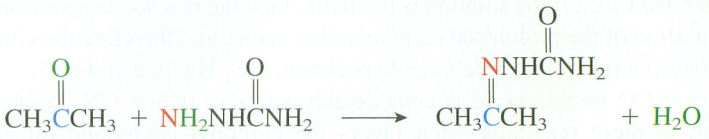
In the case of aldehydes and ketones, several C=N forming reactions were used to make derivatives. The most common of these are shown in the following equations. Note that each reagent has an electronegative group substituted on the NH_2. This helps shift the equilibrium toward the product and makes it more likely to be a solid. Tables of the melting points of these derivatives for common aldehydes and ketones can be found in many reference books.

The reaction of an aldehyde or a ketone with **hydroxylamine** produces an **oxime** derivative:

Hydroxylamine

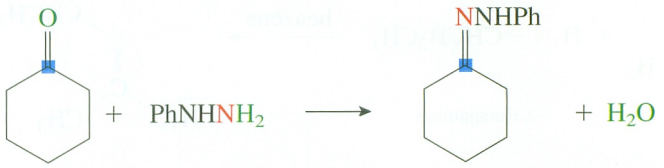
mp: 57–58°C
An oxime

The reaction of an aldehyde or a ketone with **semicarbazide** produces a **semicarbazone** derivative:



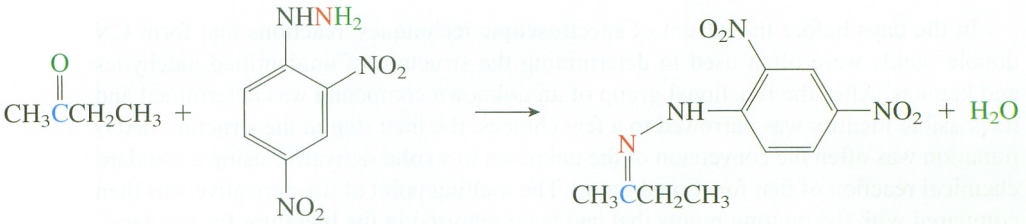
Semicarbazide — mp: 187°C, A semicarbazone

The reaction of an aldehyde or a ketone with **phenylhydrazine** produces a **phenylhydrazone** derivative:



Phenylhydrazine — mp: 77°C, A phenylhydrazone

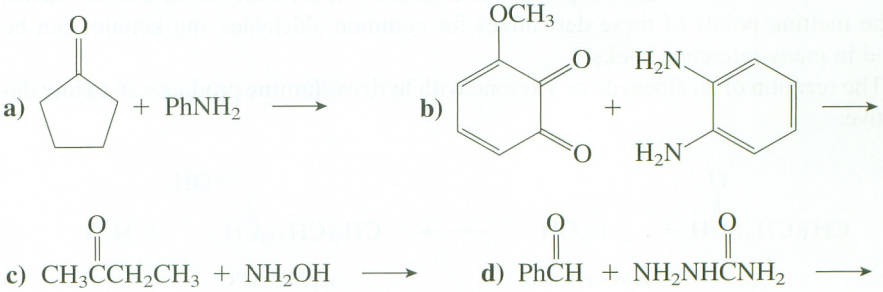
The reaction of an aldehyde or a ketone with **2,4-dinitrophenylhydrazine** produces a **2,4-dinitrophenylhydrazone** derivative. This reaction is also used as a test for the presence of an aldehyde or ketone. A drop or two of a suspected aldehyde or ketone is added to a solution of 2,4-dinitrophenylhydrazine in ethanol and water. The formation of a precipitate, usually orange or red, of the derivative indicates that the unknown is an aldehyde or ketone:

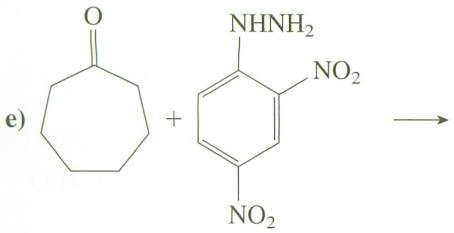


2,4-Dinitrophenylhydrazine — mp: 117°C, A 2,4-dinitrophenylhydrazone

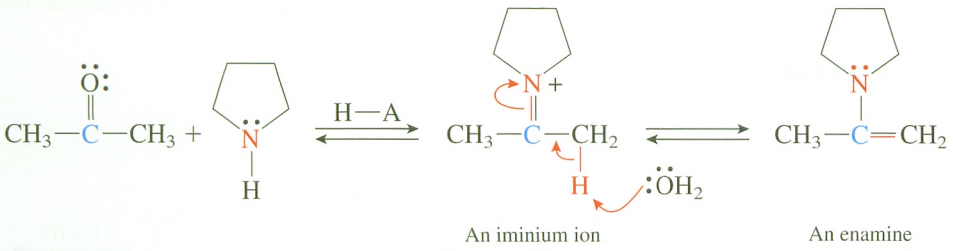
PROBLEM 18.16

Show the products of these reactions:

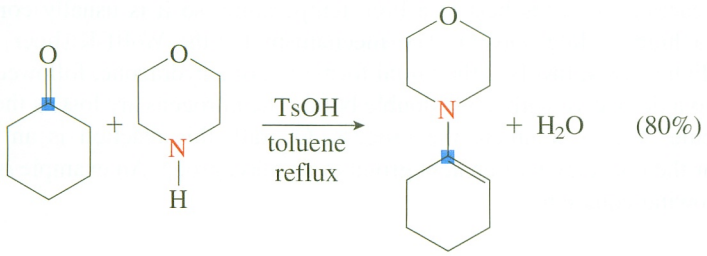


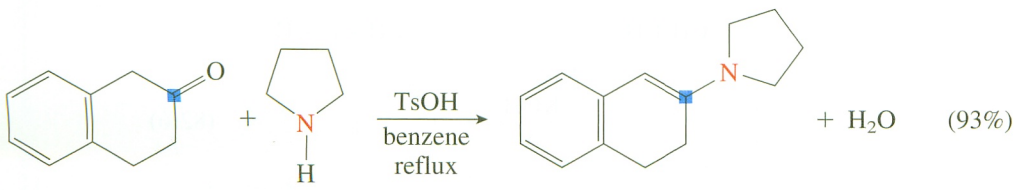
e) 

So far, all of the examples have involved primary amines. The reaction of ammonia with aldehydes and ketones also forms imines, but the products are unstable and cannot usually be isolated. If a secondary amine is used, an enamine, rather than an imine, is formed. An **enamine** has an amino group bonded to one of the carbons of a CC double bond. It is related to the imine in the same manner as an enol is related to a ketone (see Section 11.6). The mechanism for its formation can be outlined as follows:



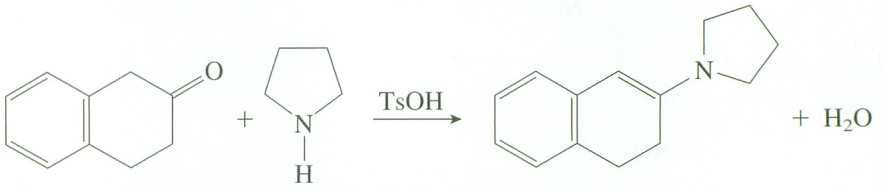
The reaction of an aldehyde or a ketone with a secondary amine follows exactly the same mechanism as the reaction with a primary amine (see Figure 18.3) until the final step. Unlike the case with a primary amine, the nitrogen of the iminium ion does not have a proton that can be removed to produce a stable imine. Therefore, a proton is removed from an adjacent carbon, resulting in the formation of an enamine. Enamine formation is illustrated in the following equations. In each case the equilibrium is driven toward the products by removal of water.





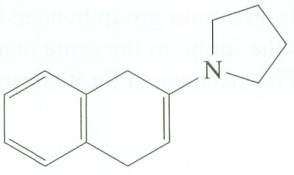
PROBLEM 18.17

Show all of the steps in the mechanism for this reaction:



PROBLEM 18.18

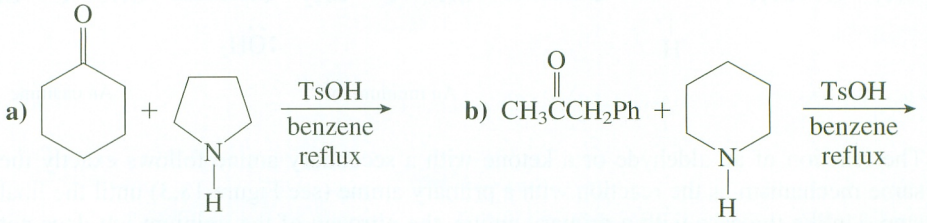
Explain why the reaction in problem 18.17 produces the enamine shown in that equation rather than the following enamine:



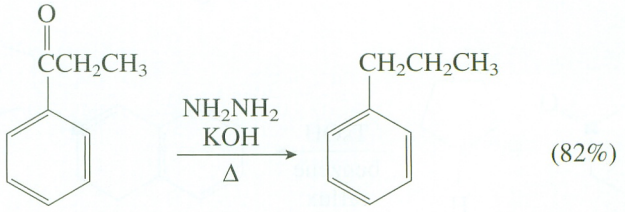
Not formed

PROBLEM 18.19

Show the products of these reactions:



The Wolff-Kishner reduction (see Section 17.13) is a useful reaction that involves an imine as an intermediate. In this procedure the carbonyl group of an aldehyde or ketone is converted to a CH_2 group by treatment with hydrazine and potassium hydroxide. The reaction proceeds best at a high temperature, so it is usually conducted at reflux in a high boiling solvent. The mechanism for the Wolff-Kishner reduction, shown in Figure 18.4, involves the initial formation of a hydrazone, followed by isomerization to a derivative with a NN double bond. The nitrogens are lost as the very stable molecule, N_2, to complete the process. Overall, this reaction is an important method for the conversion of an acyl group to an alkyl group. An example is provided in the following equation:



(82%)

1-Phenyl-1-propanone (propiophenone)

Propylbenzene

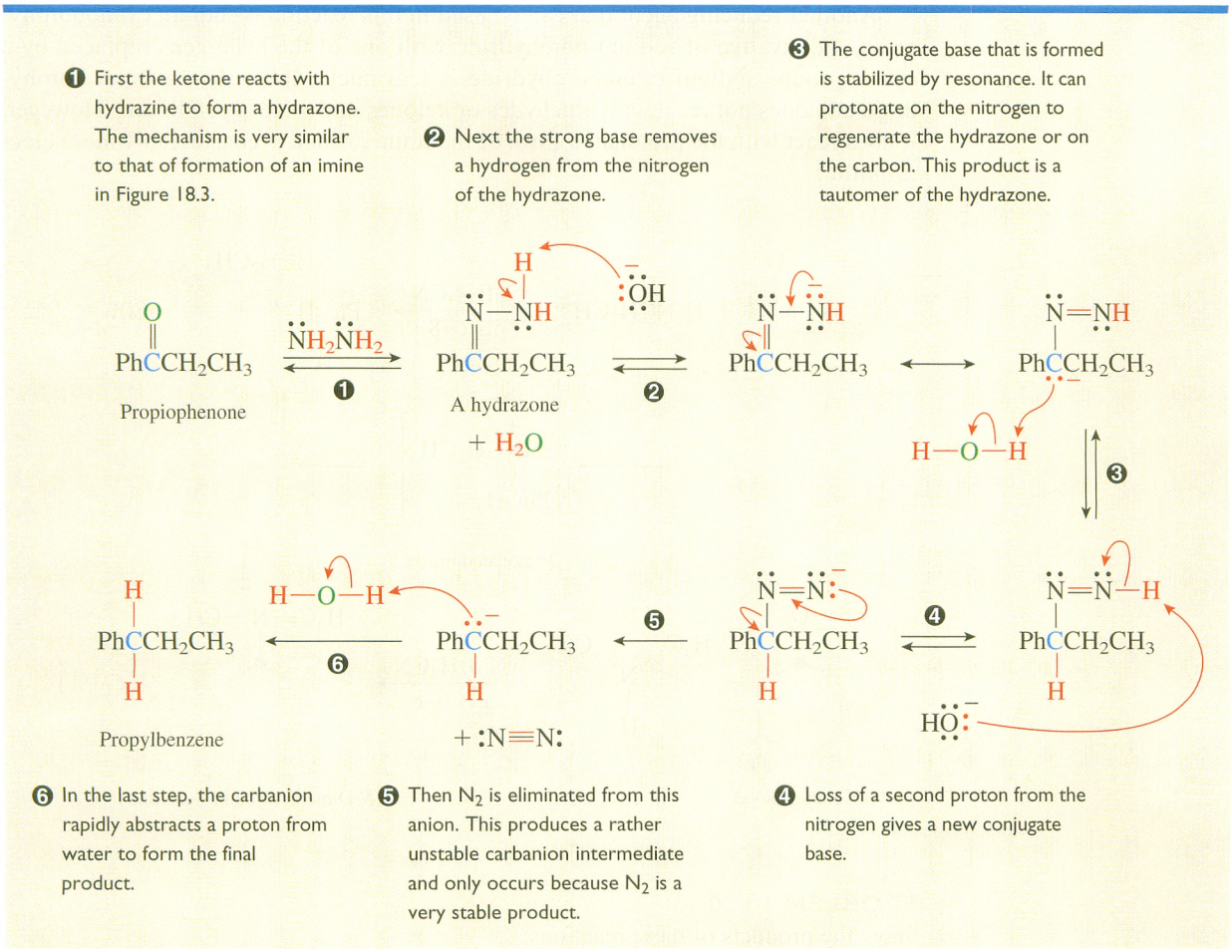
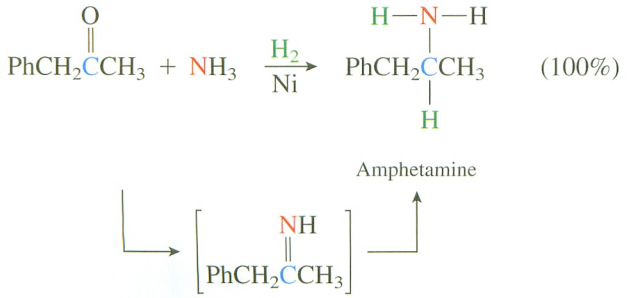


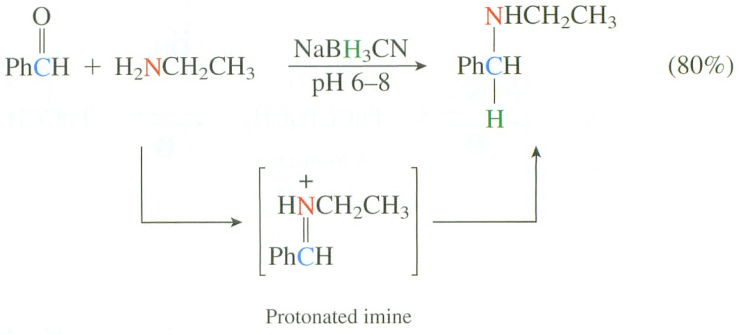
Figure 18.4

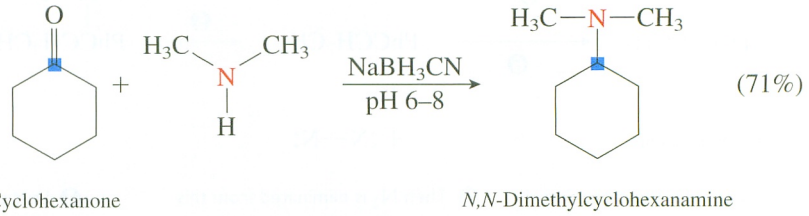
MECHANISM OF THE WOLFF-KISHNER REDUCTION.

Imines are also intermediates in a useful process called reductive amination. In this reaction an aldehyde or a ketone is reacted with an amine to form an imine. A reducing agent, such as hydrogen and a catalyst, is also present in the reaction mixture. The reducing agent chosen is one that will not reduce the carbonyl compound but will reduce the more reactive imine. The imine is reduced as rapidly as it is formed and is not isolated. The reaction is illustrated in the following equation:



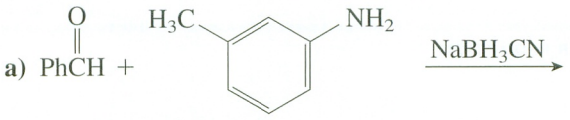
Another reducing agent that can be used in this reaction is sodium cyanoborohydride, a derivative of sodium borohydride with one of the hydrogens replaced by a cyano group. Sodium cyanoborohydride is less nucleophilic than sodium borohydride and does not react with aldehydes or ketones under these conditions. However, it does react with the protonated form of the imine, which is considerably more electrophilic:

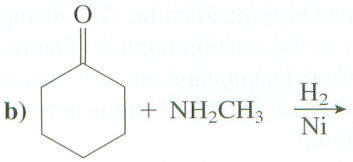


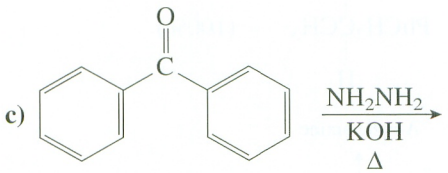


PROBLEM 18.20

Show the products of these reactions:





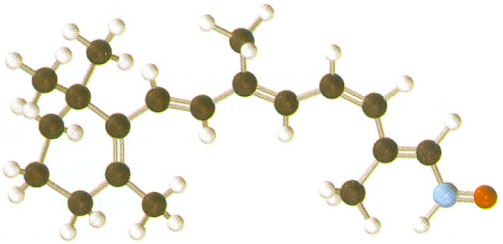


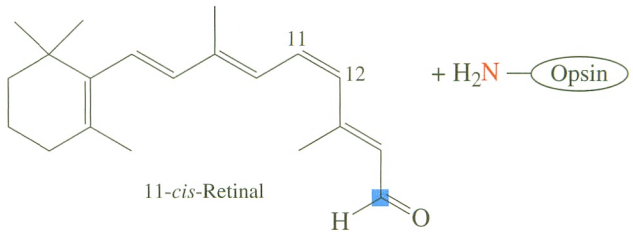
Focus On Biological Chemistry

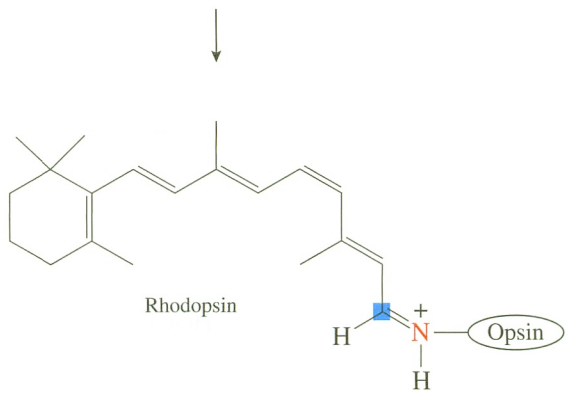
Imines in Living Organisms

Imines are readily formed from amines and aldehydes or ketones under physiological conditions. In addition, they are readily hydrolyzed back to the amine and the carbonyl compound. These properties provide a common way in biochemical reactions to temporarily link an aldehyde or a ketone to a protein by reacting the carbonyl with a free amino group of the protein to form an imine.

One example of this process is found in the chemistry of vision. In the rods and cones of the eye, the aldehyde 11-*cis*-retinal forms an imine by reaction with an amino group of the protein opsin. Studies have shown that the nitrogen of the imine of the product, called rhodopsin, is protonated.





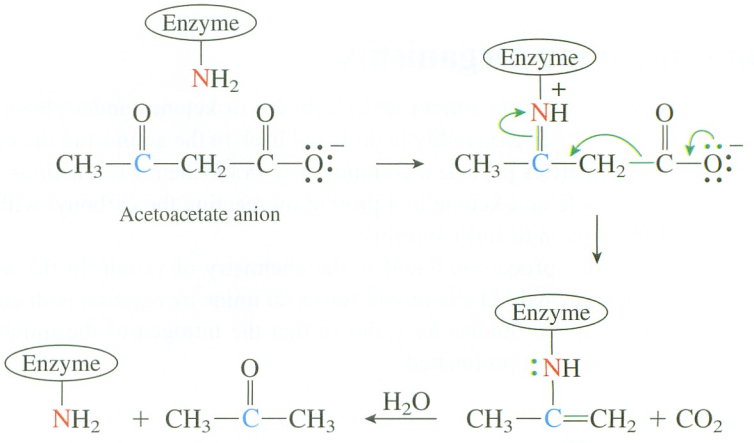


When rhodopsin absorbs light in the vision process, the cis double bond between carbons 11 and 12 isomerizes to a trans double bond. This isomerization triggers a nerve impulse telling the brain that light has been absorbed by the eye. The imine of the isomerized product is unstable and is hydrolyzed to opsin and the all-*trans* form of retinal (also known as vitamin A aldehyde). All-*trans* retinal is converted back to 11-*cis*-retinal by enzymes so that it can be used again in rhodopsin formation.

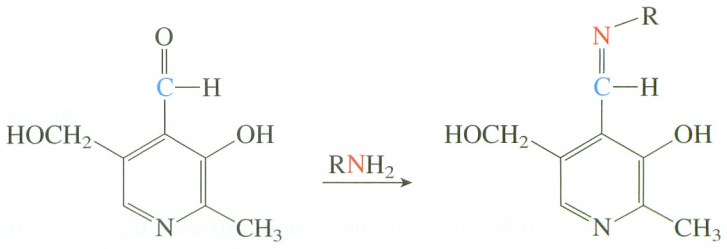
Imine formation is also important in the enzymatic decarboxylation of acetoacetate anion to form acetone, which occurs during the metabolism of glucose. Initial

Continued

formation of a protonated imine facilitates the loss of carbon dioxide to form an enamine. Hydrolysis of the enamine produces acetone and regenerates the enzyme catalyst:



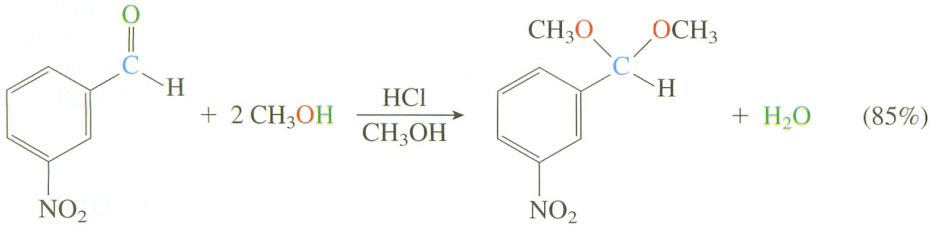
Many enzymes require the presence of an additional compound, called a coenzyme, to carry out their catalytic functions. The coenzyme often bonds to the substrate, modifying its structure so that the enzyme can more easily accomplish its catalytic reaction. Pyridoxal, also known as vitamin B_6, acts as a coenzyme by forming an imine between its aldehyde group and an amine group of the substrate. In these biological reactions it is important that the equilibrium constant for imine formation not be too large so that the CN double bond can be cleaved by hydrolysis when the reaction is finished, thus completing the catalytic cycle. The compounds that are used to form derivatives of carbonyl compounds—hydroxylamine, hydrazine, phenylhydrazine, and semicarbazide—are poisonous because they form imine derivatives of pyridoxal. The equilibrium constant for the formation of these derivatives is so large that there is not enough free pyridoxal available to carry out its catalytic functions.



Pyridoxal
(vitamin B_6)

18.9 ADDITION OF ALCOHOLS

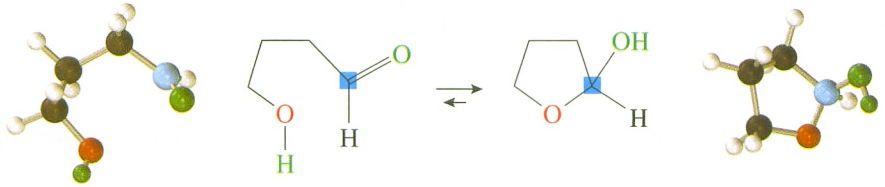
Aldehydes and ketones add two equivalents of alcohols to form **acetals.** (The term *ketal,* which was formerly used to describe the product formed from a ketone, may still be encountered.)



m-Nitrobenzaldehyde An acetal

The mechanism for this reaction, shown in Figure 18.5, is as long as any that you will encounter in this text. You can make the task of learning this mechanism much easier by recognizing its similarities to other mechanisms in this chapter and the similarities among the steps within this mechanism. The initial addition follows the acidic conditions mechanism. Steps 1, 2, and 3 are nearly identical to the mechanism for acid-catalyzed hydration (Section 18.3) with the exception that the nucleophile is the oxygen of methanol rather than the oxygen of water. The addition product, a **hemiacetal,** is similar to the hydrate or the carbinolamine. Steps 4 and 5 are very similar to steps in imine formation (Figure 18.3). First the oxygen is protonated, and then water leaves with the help of the unshared electrons on the other oxygen. However, in contrast to imine formation, the product of step 5 cannot be stabilized by the loss of a proton. Instead, the oxygen of a second molecule of alcohol acts as a nucleophile.

Like hydrates, hemiacetals are not favored at equilibrium and, in general, cannot be isolated. The equilibrium is shifted in their favor by the inductive effects of electron-withdrawing groups, similar to the case of hydrates. In addition, the equilibrium is shifted in their favor if the alcohol nucleophile and carbonyl electrophile are part of the same molecule as in the following example:



11.4% 88.6%

A cyclic hemiacetal

In this example the oxygen of the hydroxy group acts as an intramolecular nucleophile. Recall from Section 8.13 that intramolecular reactions are favored by entropy. Therefore, the formation of a cyclic hemiacetal has a larger equilibrium constant than a comparable intermolecular reaction. This reaction is especially important in the area of carbohydrates (sugars) because sugars contain both carbonyl and hydroxy functional

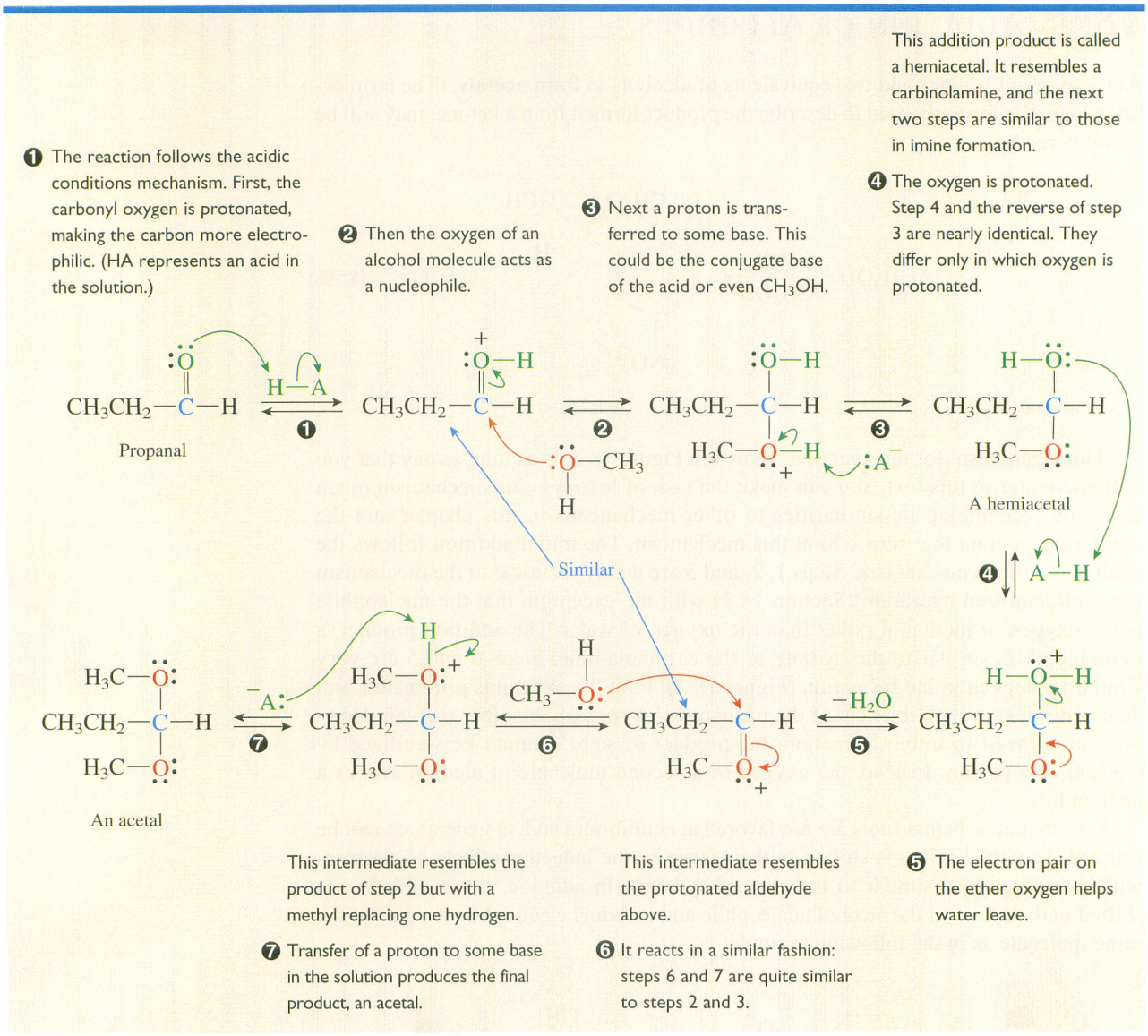
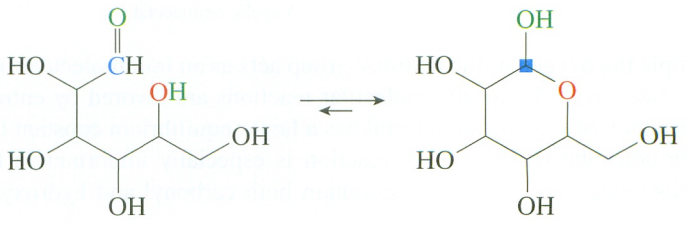


Figure 18.5

MECHANISM OF THE FORMATION OF AN ACETAL.

ORGANIC Chemistry Now™ Click *Mechanisms in Motion* to view the **Mechanism of Acetal Formation.**

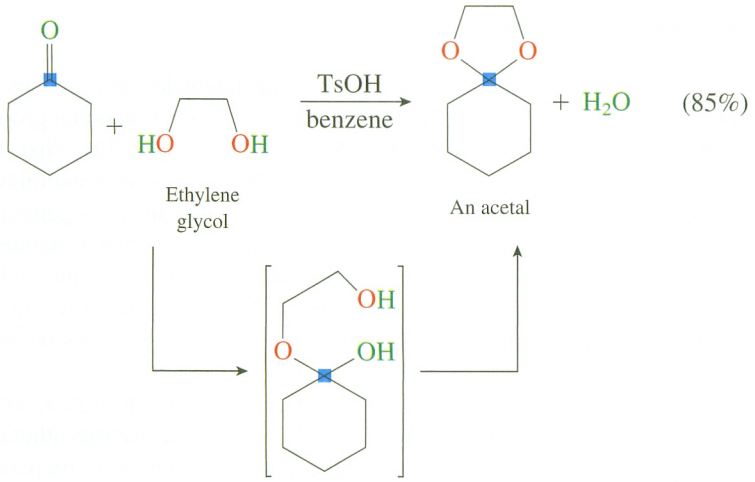
groups. For example, in aqueous solution, glucose exists almost entirely (~99.98%) as the cyclic hemiacetal:



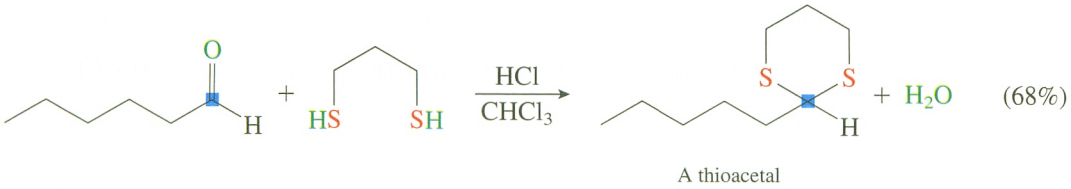
PROBLEM 18.21

Explain which of these compounds has more cyclic hemiacetal present at equilibrium:

The equilibrium between an aldehyde or a ketone and an acetal usually favors the aldehyde or ketone. Therefore, to prepare an acetal, the equilibrium must somehow be driven toward the product. This is usually accomplished by removing the water that is formed as a by-product. Acetals are stable in the absence of acid, because the reverse of step 7 (see Figure 18.5) is a protonation and cannot occur under basic or neutral conditions. Once the equilibrium has been driven to completion, the reaction mixture is neutralized and the products can then be isolated. Often a diol, such as ethylene glycol, is used in the preparation of acetals. In such cases the reaction is more favorable because the conversion of the hemiacetal to the acetal is intramolecular.

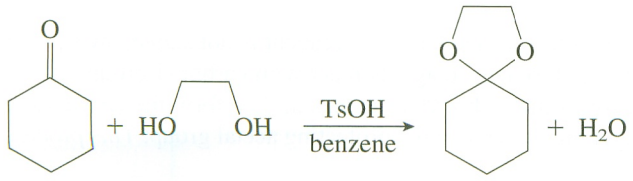


Similar chemistry can be used to prepare thioacetals. In Chapter 20, we will examine an important carbon nucleophile that can be generated from thioacetals.



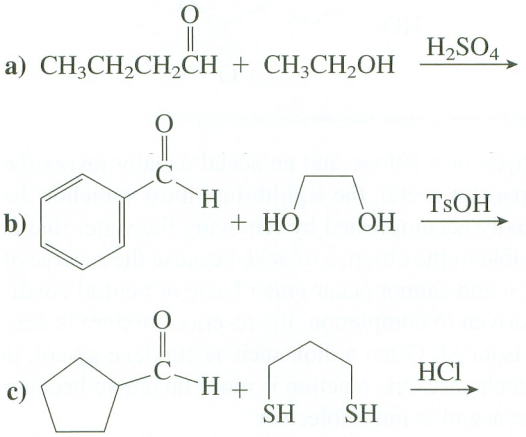
PROBLEM 18.22

Show all of the steps in the mechanism of this reaction:



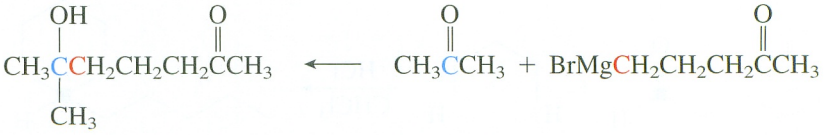
PROBLEM 18.23

Show the products of these reactions:



A major use of acetals is as protecting groups for aldehydes and ketones. A protecting group is used to prevent a reagent from reacting with one functional group while it reacts with another functional group somewhere else in the molecule. First, the protecting group is put on one of the functional groups. After the desired reaction has been performed elsewhere in the molecule, the protecting group is removed, regenerating the original functional group. Aldehydes and ketones are readily converted to acetals. Many reagents that would react with the carbonyl compound do not react with acetals, because this group is stable to nucleophiles and bases. After the desired reaction is accomplished, the carbonyl group can readily be regenerated by hydrolysis of the acetal with aqueous acid.

Let's look at an example of the utility of protecting groups in organic synthesis. Suppose the synthetic target is 6-hydroxy-6-methyl-2-heptanone. Retrosynthetic analysis on this compound might suggest a Grignard reaction as a method to prepare the alcohol group while also forming a carbon–carbon bond:



6-Hydroxy-6-methyl-2-heptanone (synthetic target)

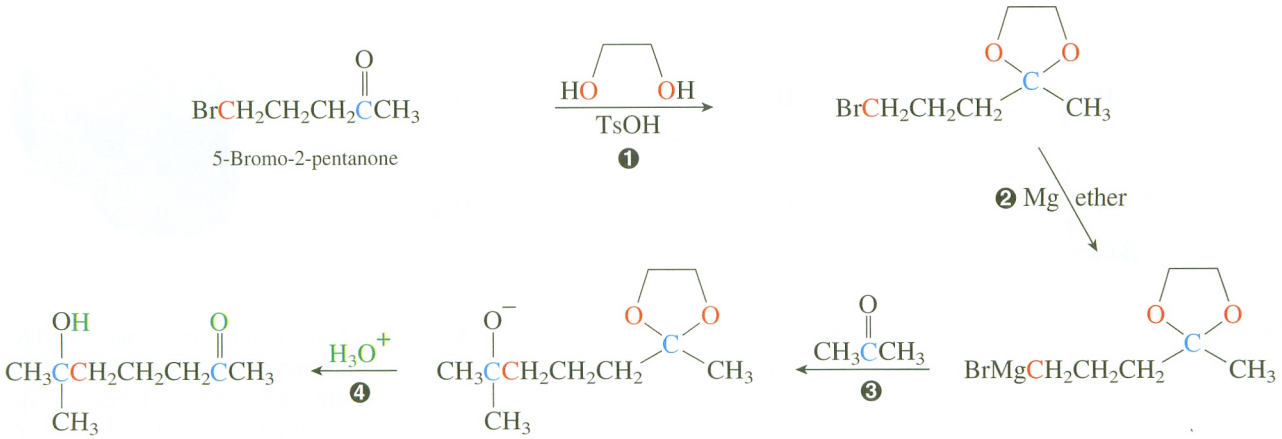
This reagent cannot be prepared because the carbonyl group and the Grignard reagent are incompatible.

The problem is that the needed Grignard reagent is not stable, owing to the presence of the carbonyl group: Grignard reagents react with carbonyl groups. The solution to the problem is to protect the carbonyl as an acetal, then form the Grignard reagent, react it with acetone, and finally remove the protecting acetal group. This process is outlined in Figure 18.6.

An attempt to form a Grignard reagent from 5-bromo-2-pentanone is doomed to failure because the Grignard will react with the carbonyl group.

❶ Therefore, the carbonyl group is first protected as an ethylene glycol acetal.

❷ Because the acetal group does not react with Grignard reagents (or other basic or nucleophilic reagents), the Grignard reagent can be prepared from this compound. The acetal is being used as a protecting group for the carbonyl group.



❹ When the reaction is worked up with aqueous acid, not only is the alkoxide group protonated but the acetal is also hydrolyzed back to the ketone and ethylene glycol. Easy removal is an important feature of protecting groups.

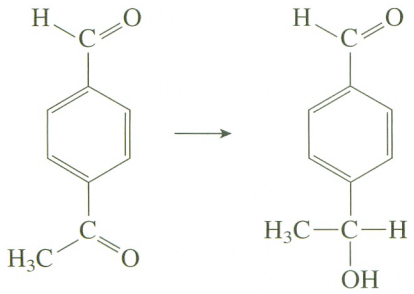
❸ This Grignard reagent reacts like any other Grignard reagent.

Figure 18.6

USE OF AN ACETAL AS A PROTECTING GROUP.

PROBLEM 18.24

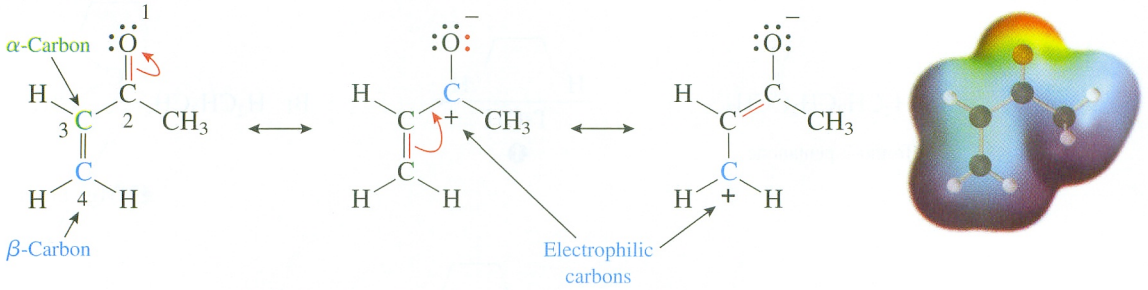
Because aldehydes are more reactive than ketones, it is possible to selectively form an acetal group at the aldehyde group without also forming one at the ketone group of a compound that contains both functional groups. Using this information, suggest how the following transformation could be accomplished:



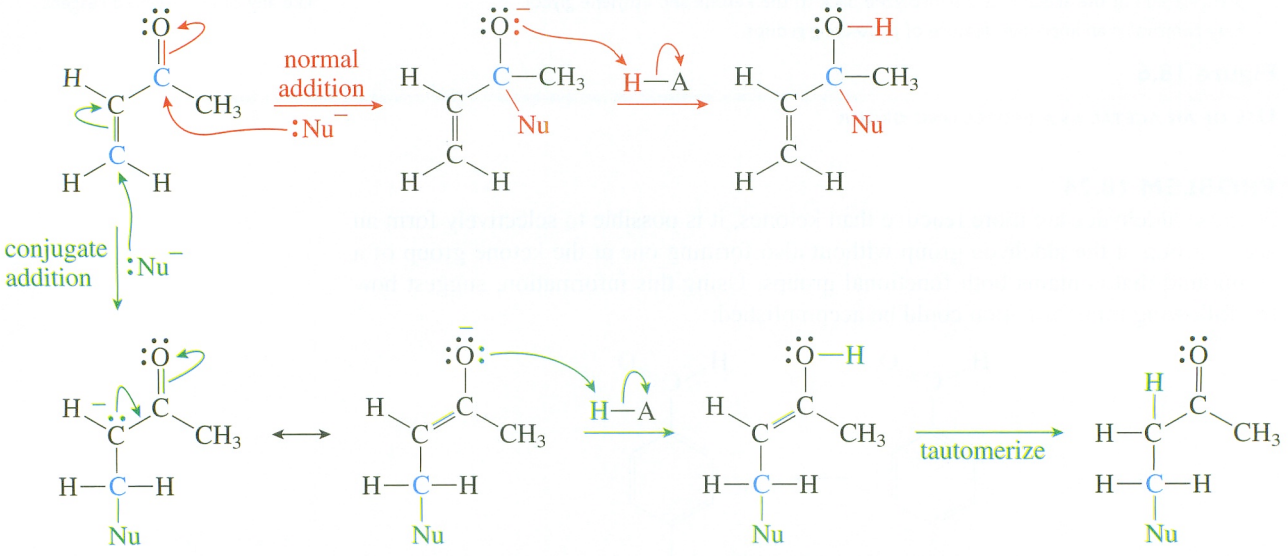
18.10 CONJUGATE ADDITIONS

When a CC double bond is conjugated with a carbonyl group, the double bond often has chemical reactions that are similar to those of the carbonyl group. (Recall from Section 12.3 that the carbon adjacent to the carbonyl group is sometimes called the

α-carbon. The next carbon is called the β-carbon, and so on. Therefore, a compound with a double bond conjugated to the carbonyl group is said to be α,β-unsaturated.) The β-carbon of an α,β-unsaturated carbonyl compound is electrophilic, very similar to the carbonyl carbon. This can best be understood by examination of the resonance structures for such a conjugated compound:



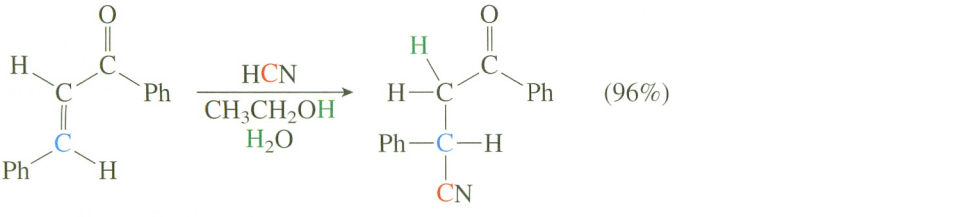
When a nucleophile reacts with an α,β-unsaturated carbonyl compound, it may bond to either of the two electrophilic carbons. If it bonds to the carbonyl carbon, the reaction is termed a normal addition or a 1,2-addition (because the nucleophile and electrophile have added to adjacent positions). If, instead, it bonds to the β-carbon, the reaction is termed a conjugate addition or a 1,4-addition. The following mechanism operates under basic conditions:

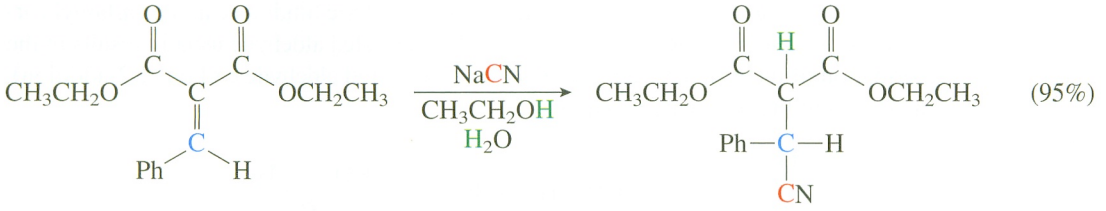


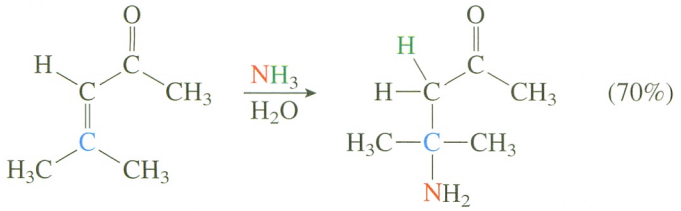
The normal addition process is identical to the other reactions that have been encountered so far in this chapter: The nucleophile bonds to the carbonyl carbon and the electrophile bonds to the oxygen of the carbonyl group. In a conjugate addition the nucleophile bonds to the β-carbon. The electrophile, a proton, can bond to either the α-carbon or the oxygen of the resonance stabilized anion. It actually reacts faster at the oxygen, producing an enol in an overall 1,4-addition. However, as discussed in Section 11.6, enols are less stable than the carbonyl tautomers, so the product that is isolated contains the carbonyl group.

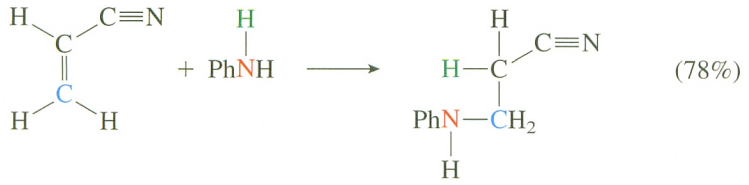
The overall result of a conjugate addition is the addition of a proton and a nucleophile to the CC double bond. However, this reaction differs greatly from the additions discussed in Chapter 11, in which the electrophile adds first. Here, the nucleophile adds in the first step. This reaction does not occur unless there is a group attached to the double bond that can help stabilize, by resonance, the carbanion intermediate. In many cases this is the carbonyl group of an aldehyde or a ketone. However, other groups, such as the carbonyl group of an ester or a cyano group, also enable this reaction to occur.

Whether a normal or a conjugate addition occurs depends on both the structure of the α,β-unsaturated electrophile and the nature of the nucleophile. The less reactive nucleophiles usually give conjugate addition because the reactions are reversible and the conjugate addition product is more stable. Thus, cyanide ion and amines add in a conjugate manner as shown in the following examples:



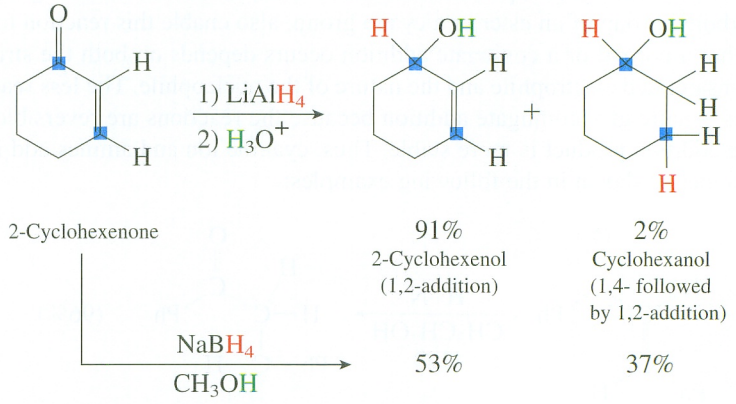




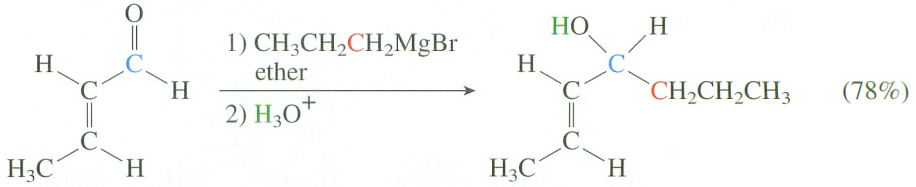


For the more reactive nucleophiles, where addition is essentially irreversible, whether 1,2-addition or 1,4-addition occurs depends on the relative rates of addition to the two electrophilic sites, the carbonyl carbon and the β-carbon. Lithium aluminum hydride usually gives predominantly 1,2-addition and provides a useful way to reduce the carbonyl group of an α,β-unsaturated compound. Sodium borohydride, on the other hand, often gives a mixture of 1,2-addition and the completely reduced product, where 1,4-addition followed by 1,2-addition has occurred. Thus, the reaction of 2-cyclohexenone with lithium

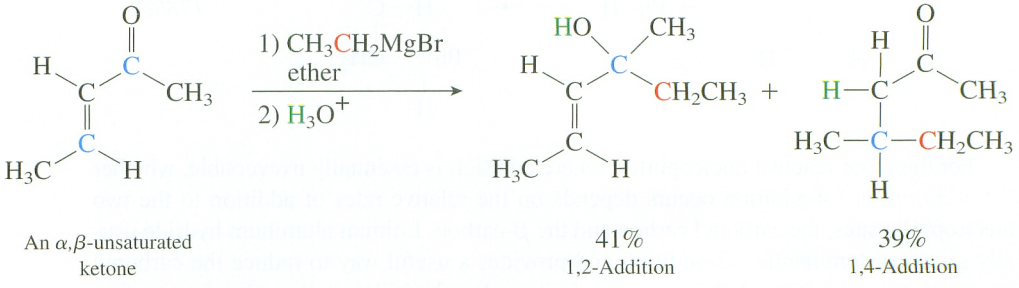
aluminum hydride gives a good yield of the 1,2-addition product, 2-cyclohexenol. In contrast, reaction with sodium borohydride is less useful because of the mixture of products that is formed. Part of the reaction occurs by 1,2-addition to produce 2-cyclohexenol and part by 1,4-addition to produce cyclohexanone, which is then reduced further to cyclohexanol.



In the case of a Grignard reagent reacting as the nucleophile, the amounts of normal addition and conjugate addition depend on the steric hindrance at the carbonyl carbon and the β-carbon. Reaction with an α,β-unsaturated aldehyde usually results in the formation of the product from attack at the unhindered aldehyde carbon (1,2-addition), as shown in the following equation:



Because of the increased steric hindrance at the carbonyl carbon, similar reactions involving α,β-unsaturated ketones often result in a mixture of 1,2- and 1,4-addition. The exact amount of each product depends on the relative amounts of steric hindrance at the two electrophilic carbons and may be difficult to predict in advance. An example is provided in the following equation:



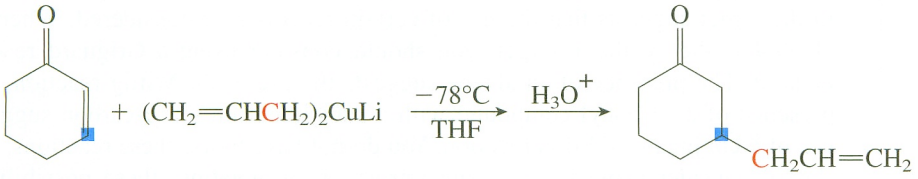
If conjugate addition of an organometallic nucleophile is desired, this can be accomplished by using a lithium diorganocuprate reagent, which has the organic group at-

tached to a copper atom. These reagents are prepared by the reaction of organolithium compounds with copper(I) salts such as cuprous iodide, as illustrated in the following equation for the preparation of lithium dimethylcuprate:

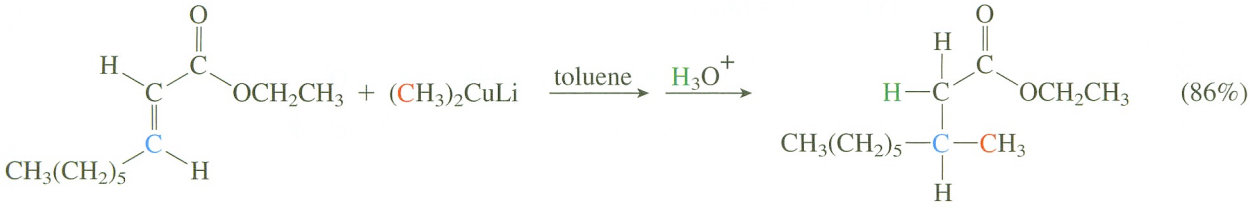
$$2\ CH_3Li + CuI \longrightarrow (CH_3)_2CuLi + LiI$$

Methyllithium — Lithium dimethylcuprate

The reactions of lithium diorganocuprates with α,β-unsaturated carbonyl compounds give excellent yields of 1,4-addition products:



(94%)



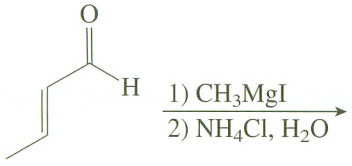
(86%)

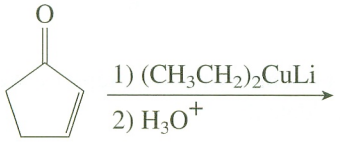
In summary, lithium aluminum hydride usually gives good yields of 1,2-addition products, that is, unsaturated alcohols. The reaction of Grignard reagents with α,β-unsaturated aldehydes also gives good yields of 1,2-addition products. Nucleophiles that give good yields of 1,4-addition products are cyanide ion, amines, and lithium diorganocuprate reagents. The cuprate reagents provide an excellent method to add a carbon nucleophile to the β-carbon of α,β-unsaturated carbonyl compounds, a process that is very useful in synthesis.

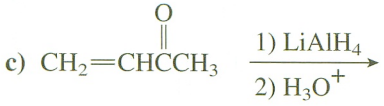
PROBLEM 18.25

Show the products of these reactions:

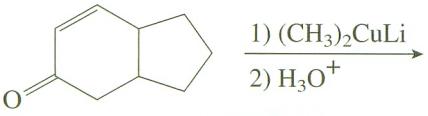
ORGANIC Chemistry Now™
Click *Coached Tutorial Problems* to practice **Conjugate Addition Reactions.**

a) 

b) 

c) 

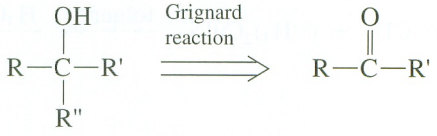
d) 

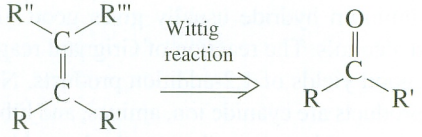
e) 

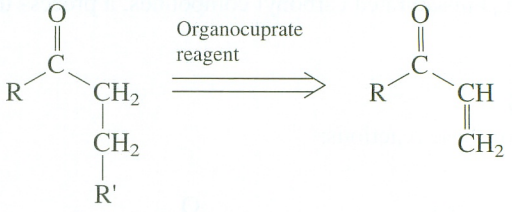
18.11 SYNTHESIS

By now, you should be fairly comfortable using retrosynthetic analysis to design the synthesis of a target molecule. Remember that carbon–carbon bond forming reactions are especially important in synthesis. Several extremely useful reactions that result in the formation of carbon–carbon bonds have been introduced in this chapter. These are the Grignard reaction to prepare alcohols, the Wittig reaction to prepare alkenes, and the conjugate addition of organocuprate reagents to α,β-unsaturated carbonyl compounds.

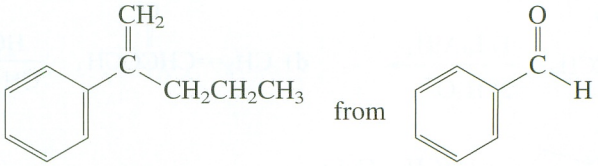
When you are designing a synthesis, the presence of certain structural features in the target suggests that the use of certain reactions be considered. Whenever an alcohol is the synthetic target, you should consider using a Grignard reaction to make it. The presence of an alkene suggests the use of the Wittig reaction, and the presence of a carbonyl compound with a substituent on the β-carbon suggests the use of a conjugate addition reaction. You do not have to use these reactions, but you should consider using them. Using retrosynthetic notation, these possibilities are summarized as follows:





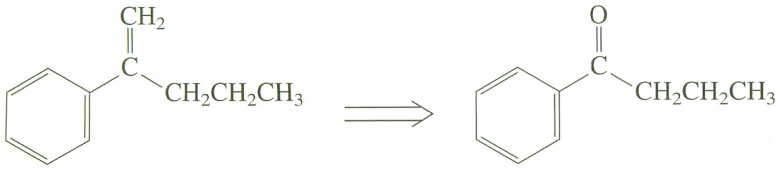


Let's try some syntheses. Suppose we need to prepare 2-phenyl-l-pentene, starting from benzaldehyde:

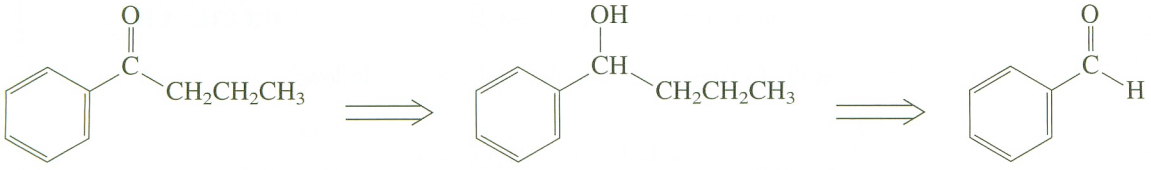


2-Phenyl-1-pentene Benzaldehyde

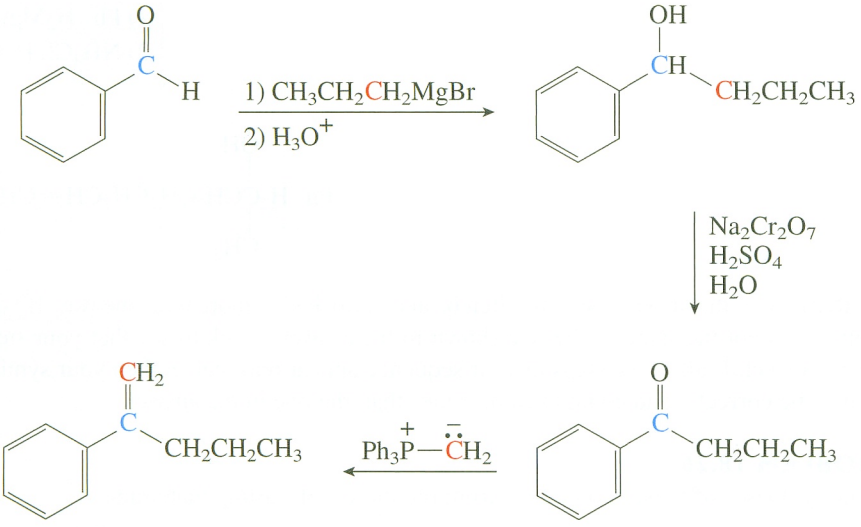
Applying retrosynthetic analysis, the presence of the alkene group in the target suggests using a Wittig reaction in its preparation.



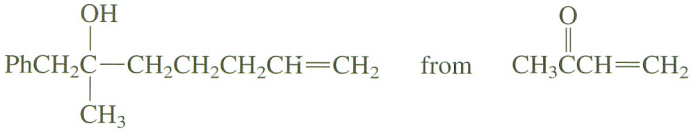
The new target is a ketone. We need to somehow add a propyl group to the carbonyl carbon of benzaldehyde to make this ketone. At this point we do not know of a reaction that will accomplish this transformation directly, but we recognize that a ketone can be prepared by oxidation of an alcohol. We can prepare the alcohol using the Grignard reaction. Our retrosynthetic analysis is as follows:



We are now ready to write the synthesis in the forward direction:



Let's try another example. This time our task is to prepare 2-methyl-1-phenylhept-6-en-2-ol from but-3-en-2-one.

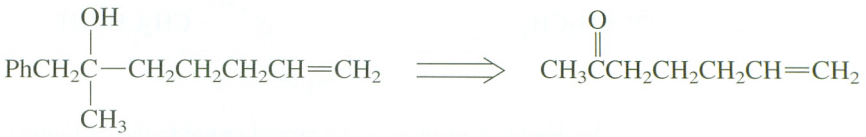


2-Methyl-1-phenylhept-6-en-2-ol

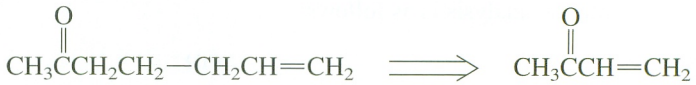
from

But-3-en-2-one

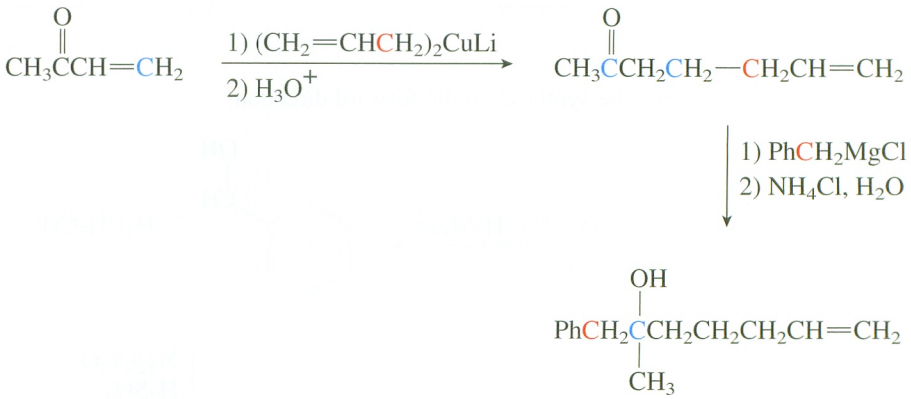
The target is an alcohol, so we should consider using a Grignard reaction. Any of the three groups attached to the carbon bonded to the hydroxy group could potentially be attached. Comparison of the target to but-3-en-2-one suggests that the benzyl group be added in the Grignard step. So the first step in our retrosynthetic analysis is as follows:



Our new target is a ketone that is related to but-3-en-2-one by the presence of an allyl group on the β-carbon. This suggests the use of a conjugate addition reaction:



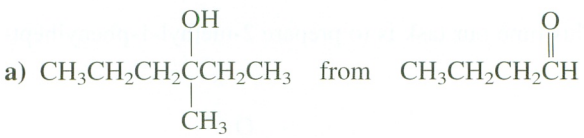
Written in the forward direction, the synthesis is as follows:

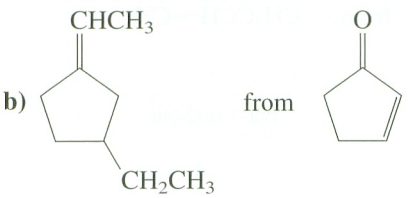


Remember that a synthesis can often be accomplished in more than one way. If your synthesis is not the same as the one shown in the answer, check to see that your steps are all correct. If all of the steps in your sequence appear reasonable, then your synthesis may be correct—and could even be better than the one in the answer.

PROBLEM 18.26

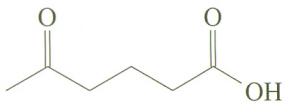
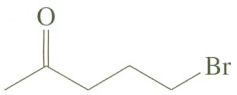
Show syntheses of these compounds from the indicated starting materials:





c) $CH_3\overset{\overset{CH_2}{\|}}{C}CH_2CH_2CH_2CH_3$ from $HC\overset{\overset{O}{\|}}{C}H{=}CH_2$

d)  from

e)  from 

Review of Mastery Goals

After completing this chapter, you should be able to:

- Show the products resulting from the addition to aldehydes and ketones of all of the reagents discussed in this chapter. (Problems 18.27, 18.28, 18.32, 18.33, and 18.36)
- Show the products resulting from the addition of certain of these reagents to α,β-unsaturated compounds, noting whether 1,2- or 1,4-addition predominates. (Problems 18.29, 18.32, and 18.36)
- Show the mechanisms for any of these additions. (Problems 18.39, 18.41, 18.45, 18.47, 18.48, and 18.52)
- Predict the effect of the structure of the aldehyde or ketone on the position of the equilibrium for these reactions. (Problems 18.30, 18.31, 18.34, 18.35, 18.58, and 18.59)
- Use these reactions, in combination with the reactions from previous chapters, to synthesize compounds. (Problems 18.38, 18.42, and 18.43)
- Use acetals as protecting groups in syntheses. (Problem 18.43)

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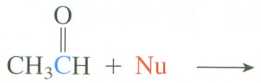
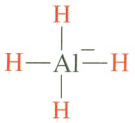
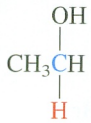
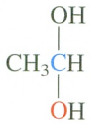
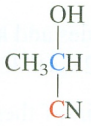
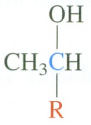
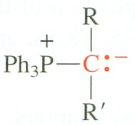
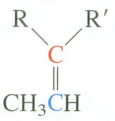
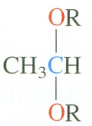
Click *Mastery Goal Quiz* to test how well you have met these goals.

Visual Summary of Key Reactions

The reactions in this chapter begin with the addition of a nucleophile to the carbon of a carbonyl group and an electrophile, usually a proton, to the oxygen. Under basic conditions the nucleophile adds first, whereas the proton adds first under acidic conditions. Depending on the nature of the nucleophile, the reaction may stop at this stage or proceed further. Figure 18.7 summarizes the mechanisms followed by the various nucleophiles. Table 18.2 lists the nucleophiles and the products that result from their reactions with aldehydes and ketones.

Table 18.2 Additions to the Carbonyl Group

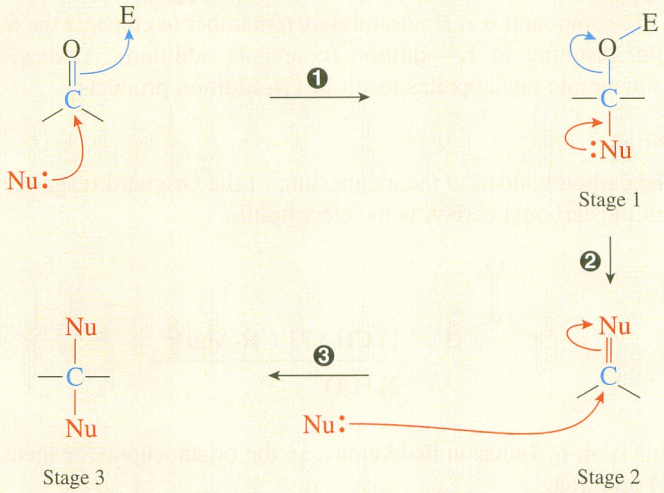


Nucleophile	Product	Comments
		**Section 18.2** Reaction with $NaBH_4$ or $LiAlH_4$ proceeds to stage 1 (see Figure 18.7) and follows the basic conditions mechanism.
H_2O		**Section 18.3** This reaction proceeds to stage 1. Hydrates usually cannot be isolated because of the unfavorable equilibrium. The reaction follows either the acidic or basic conditions mechanism.
HCN		**Section 18.4** This reaction proceeds to stage 1 and follows the basic conditions mechanism.
R—MgX		**Section 18.6** Reaction with organometallic nucleophiles (Grignard reagents and organolithium reagents) proceeds to stage 1 and follows the basic conditions mechanism.
		**Section 18.7** The Wittig reaction proceeds to stage 2 and follows the basic conditions mechanism.
RNH_2		**Section 18.8** Imine formation proceeds to stage 2 with primary amines. Addition follows the basic conditions mechanism, but acid is needed to remove the oxygen. Secondary amines give enamines.
ROH		**Section 18.9** Acetals are formed at stage 3. Thiols react in a very similar manner. The unfavorable equilibrium must be driven to products. The reaction follows the acidic conditions mechanism.

❶ All of these reactions begin this way. The electrophile (E) is usually hydrogen, but in the case of the Wittig reaction, it is phosphorus. Under basic conditions, Nu adds first. Under acidic conditions, E (a proton) adds first.

The reaction stops at stage 1 if the original Nu has only one unshared pair of electrons (CN^-, hydrides, organometallic nucleophiles).

❷ If the nucleophile has a second pair of electrons (or can generate one), then the oxygen is eliminated. The O must be protonated first, unless E is phosphorus.



The reaction proceeds to stage 3 for alcohols and thiols as nucleophiles.

The reaction stops at stage 2 if this species is uncharged (Wittig reaction, imines).

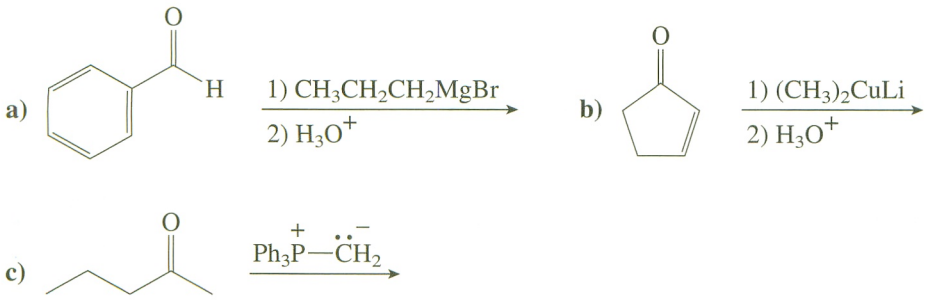
❸ When the doubly bonded Nu has a positive charge, the reaction proceeds further. If Nu is a secondary amine, a proton is lost to form an enamine. If Nu is ROH or RSH, a second Nu attacks.

Figure 18.7

MECHANISMS BEGINNING WITH ADDITION OF A NUCLEOPHILE TO A CARBONYL GROUP.

Integrated Practice Problem

Show the products of these reactions:



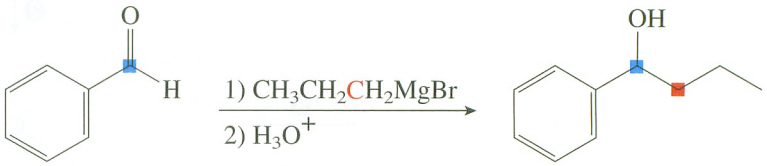
Strategy

As usual, the best strategy is to identify the nucleophile and the electrophile. This chapter introduced a new electrophile, the carbonyl carbon of an aldehyde or ketone. The nucleophiles are listed in Table 18.2. Hydride, water, HCN, and organometallic nucleophiles result in the addition of the nucleophile to the carbon and a hydrogen to the oxygen of the carbonyl group. Ylides and nitrogen nucleophiles result in the formation of a double bond between the carbonyl carbon and the nucleophile. And alcohols and thiols add two nucleophiles to the carbonyl carbon.

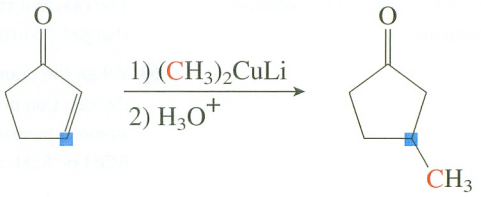
If the compound is α,β-unsaturated, remember to consider the β-carbon as the electrophile, resulting in 1,4-addition (conjugate addition). Amines, HCN, and lithium diorganocuprate nucleophiles result in 1,4-addition products.

Solutions

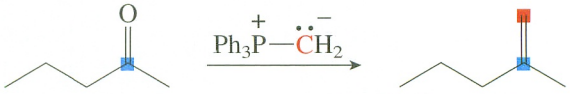
a) The carbon bonded to the magnesium of the Grignard reagent is the nucleophile and the carbonyl carbon is the electrophile.



b) This is an α,β-unsaturated ketone, so the organocuprate reagent results in a 1,4-addition.



c) The carbonyl carbon is the electrophile and the carbanion of the ylide is the nucleophile. The Wittig reaction results in a double bond between the electrophilic and nucleophilic carbons.



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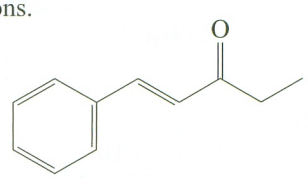
Additional Problems

18.27 Show the products of these reactions.

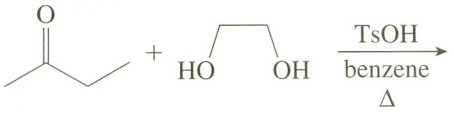
a) $PhCH_2MgBr$ → 1) CO_2 2) H_3O^+

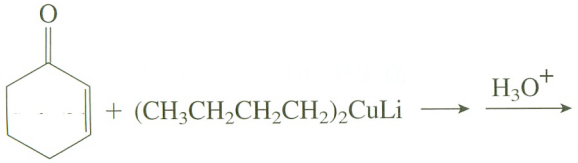
b)

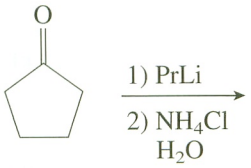


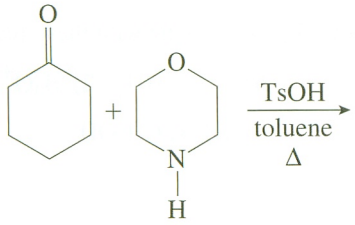
→ 1) $LiAlH_4$ 2) H_3O^+

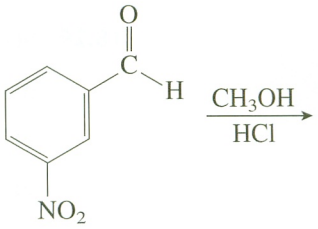
c) $CH_3CCH_3 + NH_2NHCNH_2 \xrightarrow{H_3O^+}$

d) 

e) 

f) 

g) 

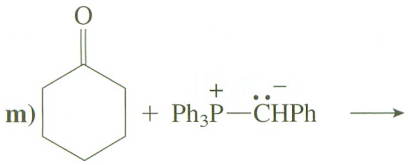
h) 

i) $Ph{-}C(=O){-}CH(CH_3){-}CHCH_3 \xrightarrow[NaBH_3CN]{CH_3NH_2}$

j) $PhCH_2Cl \xrightarrow[3)\ H_3O^+]{1)\ Mg,\ ether;\ 2)\ Ph_2CO}$

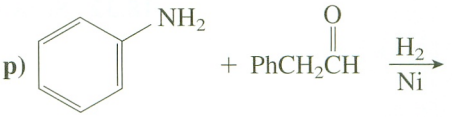
k) $CH_3CH_2CH_2CH_2CHO \xrightarrow[[CN^-]]{HCN}$

l) $CH_3CH_2CH_2CH_2CHO \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4}$

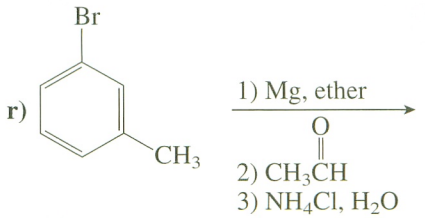
m) 

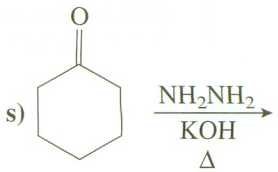
n) $PhCPh + NH_2OH \xrightarrow{H_3O^+}$

o) $PhCH{=}CHCPh \xrightarrow[H_2O\ EtOH]{KCN}$

p) 

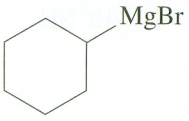
q) $HC{\equiv}C{-}C(=O){-}OCH_3 \xrightarrow[2)\ H_3O^+]{1)\ Bu_2CuLi}$

r) 

s) 

18.28 Show the products of the reactions of benzaldehyde with these reagents:

a) $NaBH_4$, CH_3OH

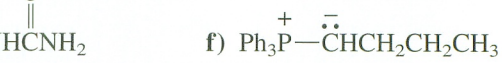
b) 1) 

2) H_3O^+

c) HCN, $[CN^-]$

d) CH_3OH, TsOH, benzene

e)

f) 

18.29 Show the products of the reactions of 3-penten-2-one with these reagents:

a) 1) CH_3Li 2) H_3O^+

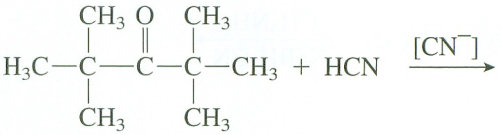
b) 1) $LiAlH_4$ 2) H_3O^+

c) 1) $(CH_3CH_2)_2CuLi$ 2) H_3O^+

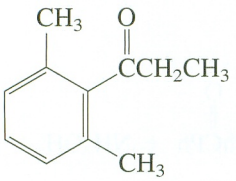
d) HCN, CH_3OH

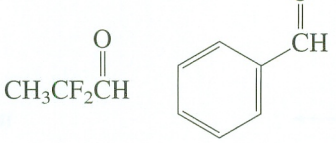
e) $PhNH_2$

18.30 Explain why this reaction gives a poor yield of the cyanohydrin product:

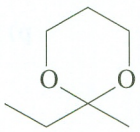


18.31 Arrange these compounds in order of increasing equilibrium constant for cyanohydrin formation and explain your reasoning:

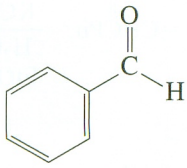




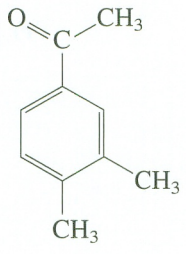
18.32 Show the products of these reactions:

a) 

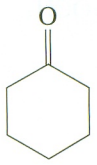
H_3O^+

b) 

HCN, $[CN^-]$

c) 

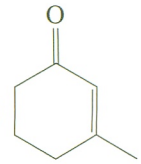
$NaBH_4$, CH_3OH

d) 

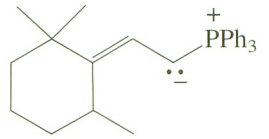
1) BuLi
2) NH_4Cl, H_2O

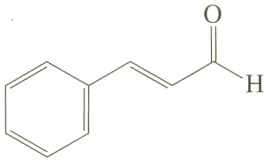
e) $PhCH{=}O + Ph_3\overset{+}{P}{-}\overset{-}{\ddot{C}}HCH{=}CH_2 \longrightarrow$

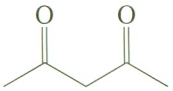
f) $PhC(=O)Ph + NH_2OH \longrightarrow$

g)  1) $(CH_3CH_2)_2CuLi$, 2) H_3O^+

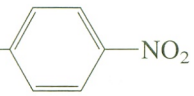
18.33 Show the products of these reactions:

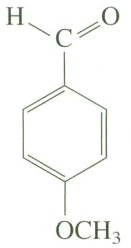
a) 

b) 

c) 

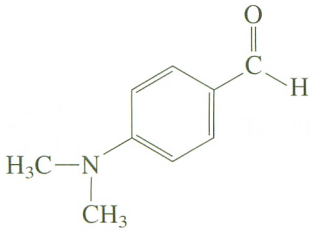
d) $CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$

e) $PhCH{=}O + NH_2NH$–  –$NO_2 \longrightarrow$

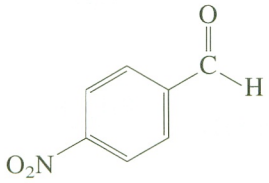
f)  + CH_2CH_2 (OH OH) 

g) $PhNH_2 + CH_2{=}CH{-}C{\equiv}N \longrightarrow$

18.34 Explain the difference in the equilibrium constants for cyanohydrin formation for these compounds:

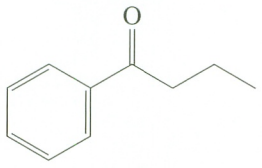
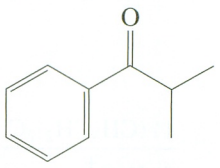


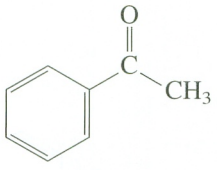
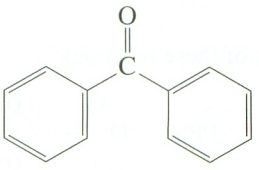
$K = 5$



$K = 1820$

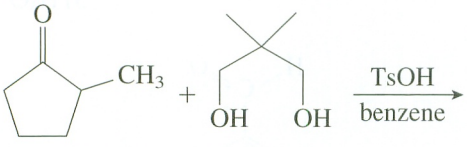
18.35 Explain which of the following compounds would have the larger equilibrium constant for cyanohydrin formation:

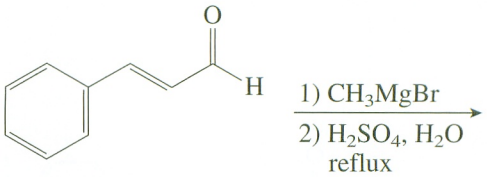
a)  or 

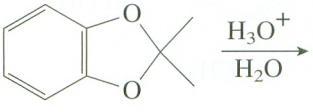
b)  or 

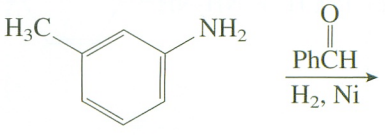
c) $CH_3\overset{O}{\overset{\|}{C}}CH_3$ or $Cl_3C\overset{O}{\overset{\|}{C}}CH_3$

18.36 Show the products of these reactions:

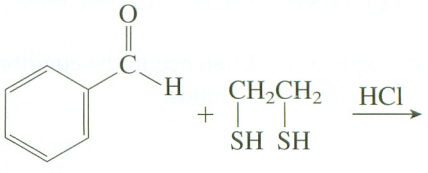
a) 

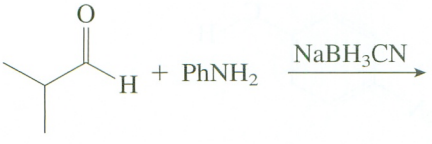
b) 

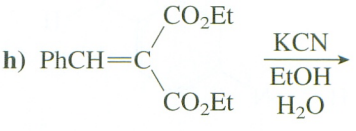
c) 

d) 

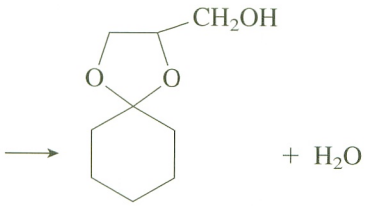
e) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H + NH_2Ph \xrightarrow[\text{benzene}]{\text{TsOH}}$

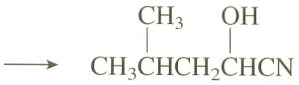
f) 

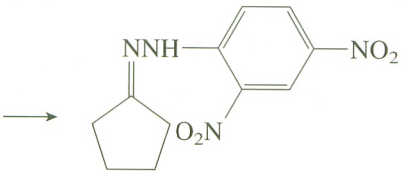
g) 

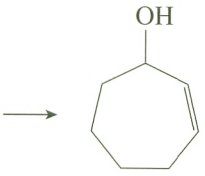
h) 

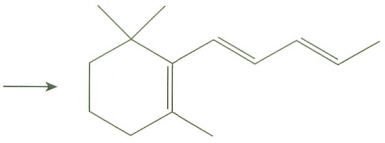
18.37 Show the aldehyde or ketone and any other reagents that are necessary to give these products:

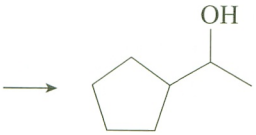
a) 

b) 

c) 

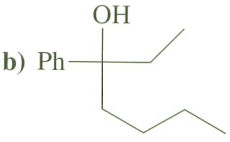
d) 

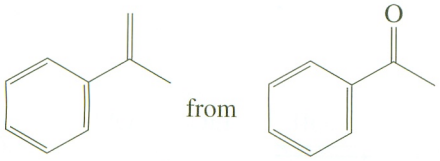
e) 

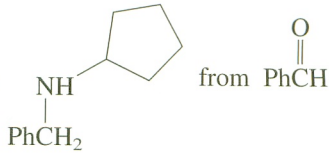
f) 

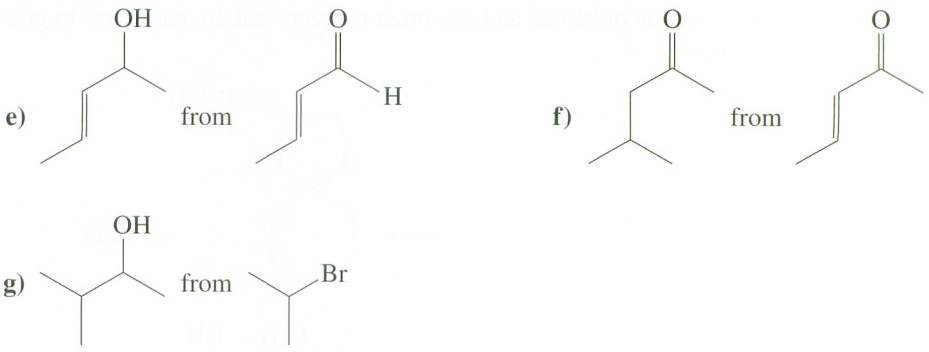
18.38 Show syntheses of these compounds from the indicated starting materials:

a) 

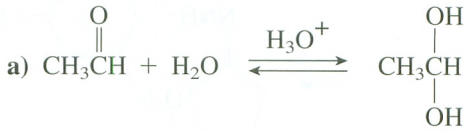
b) 

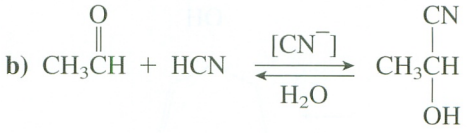
c) 

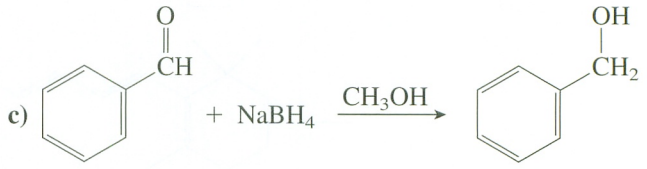
d) 

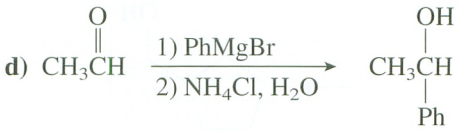


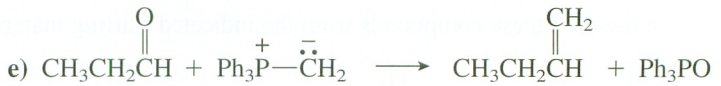
18.39 Show all the steps in the mechanisms for these reactions:

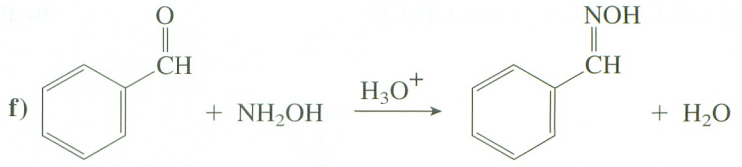


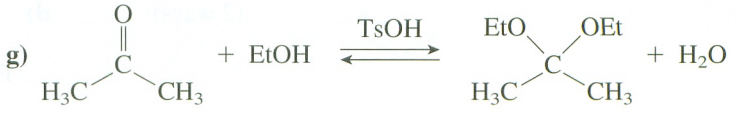












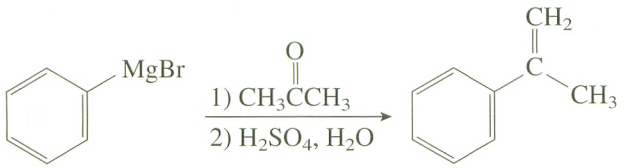
18.40 Explain why this reaction does not occur:

$$PhNH_2 + CH_2{=}CH{-}CH_3 \not\longrightarrow PhNH{-}CH_2{-}CH_2{-}CH_3$$

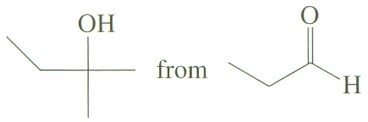
but this one does occur:

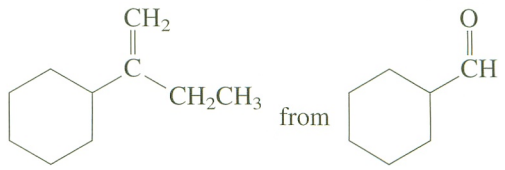
$$PhNH_2 + CH_2{=}CH{-}NO_2 \longrightarrow PhNH{-}CH_2{-}CH_2{-}NO_2$$

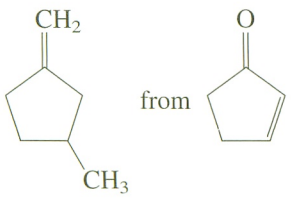
18.41 Show the steps in the mechanism for this reaction:

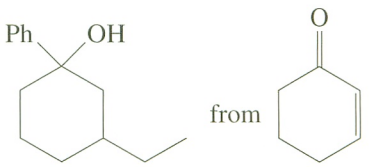


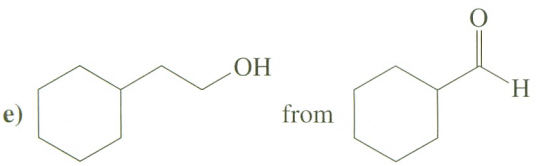
18.42 Show syntheses of these compounds from the indicated starting materials. Several steps are required. You may need to use reactions from previous chapters.

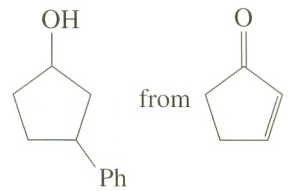
a) 

b) 

c) 

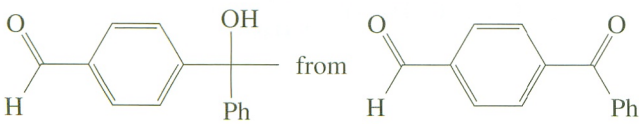
d) 

e) 

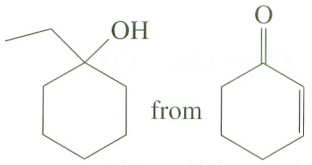
f) 

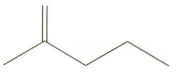
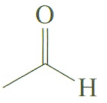
18.43 Show syntheses of these compounds from the indicated starting materials. You may need to use reactions from previous chapters.

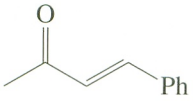
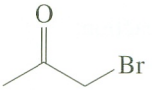
a) 

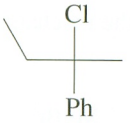
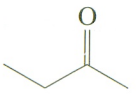
b) 

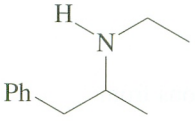
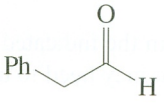
(See problem 18.24)

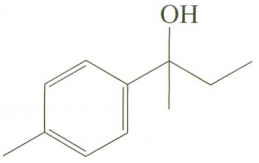
c)  from

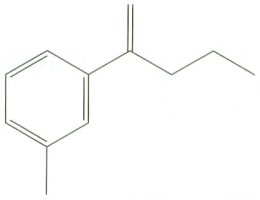
d)  from 

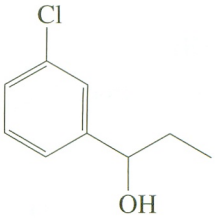
e)  from 

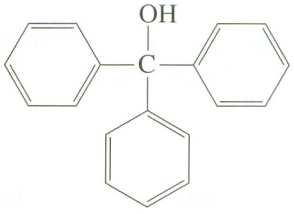
f)  from 

g)  from 

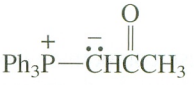
h)  from benzene

i)  from benzene

j)  from benzene

k)  from benzene

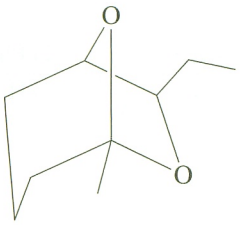
18.44 Explain why ylides such as this one can be prepared from phosphonium salts using a base such as NaOH rather than BuLi:



18.45 Explain why this reaction gives the indicated product and suggest a mechanism for its formation:

18.46 Brevicomin, an aggregation pheromone of the Western pine beetle, is an acetal. Show the structure of the dihydroxyketone that reacts spontaneously to produce brevicomin.

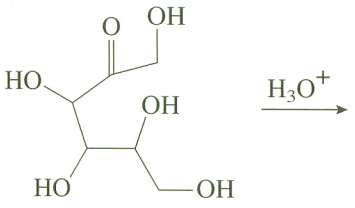
BioLink



Brevicomin

18.47 The sugar fructose is an isomer of glucose. Like glucose, fructose forms a cyclic hemiacetal, but in this case the ring is five membered rather than six membered. Show the structure for the hemiacetal formed from fructose and show a mechanism for its formation in acidic solution.

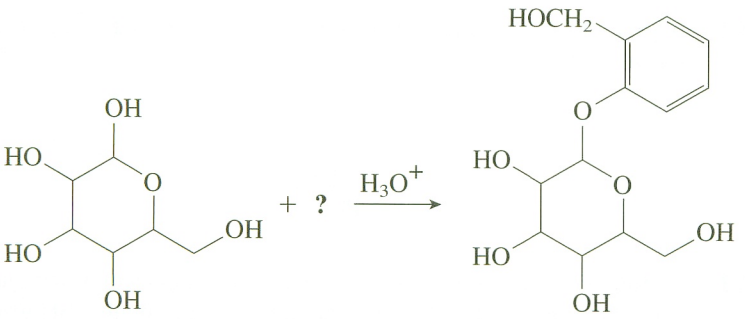
BioLink



Fructose

18.48 Glycosides are naturally occurring acetals formed from sugars and alcohols. The glycoside salicin, found in willow bark, is formed from glucose and a phenol. Show the structure of the phenol and the steps in the mechanism for the formation of salicin from glucose hemiacetal.

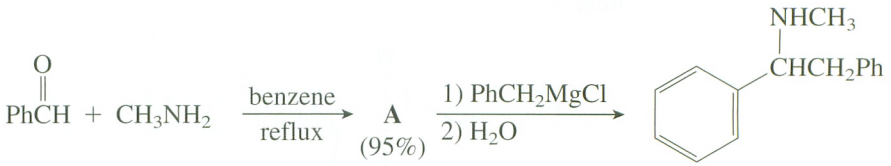
BioLink



Glucose hemiacetal

Salicin

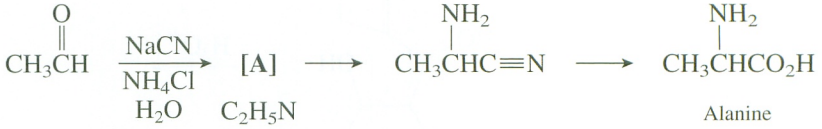
18.49 Suggest a structure for **A** in this reaction and suggest a mechanism for the conversion of **A** to **B:**



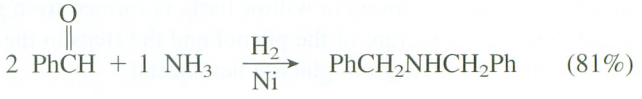
B
(96%)

BioLink

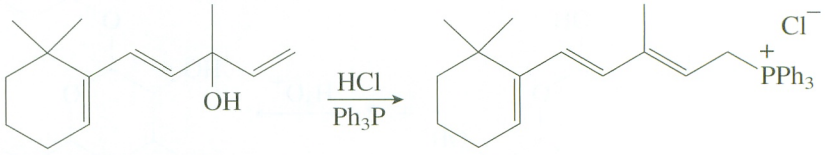
18.50 The Strecker synthesis is used to prepare amino acids in the laboratory. As shown in the following equation, an aldehyde is reacted with sodium cyanide and ammonium chloride in water to produce a cyanoamine. Conversion of the cyano group to a carboxylic acid completes the synthesis. Show the structure of the intermediate, **A,** in the following synthesis, and show the steps in the mechanism for the formation of **A** and for the conversion of **A** to the cyanoamine. (*Hint:* Remember that NH_4^+ and H_2O are in equilibrium with NH_3 and H_3O^+.)



18.51 Explain the formation of the product that results when two equivalents of benzaldehyde are reacted with one equivalent of ammonia in the presence of hydrogen and a catalyst.

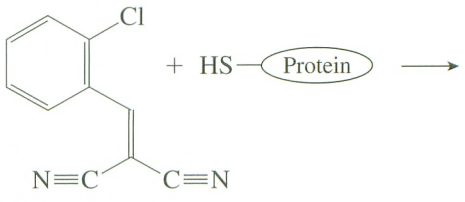


18.52 Suggest a mechanism for this reaction, which appeared in the Focus On box on page 764.



BioLink

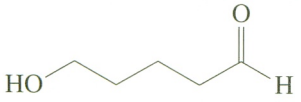
18.53 The following compound, known as CS, is a component of tear gas. It is believed that it exerts its effect by reacting with nucleophilic SH groups of proteins. Suggest a structure for the product of this reaction.



CS

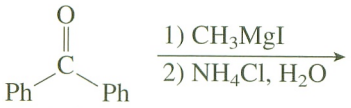
Problems Involving Spectroscopy

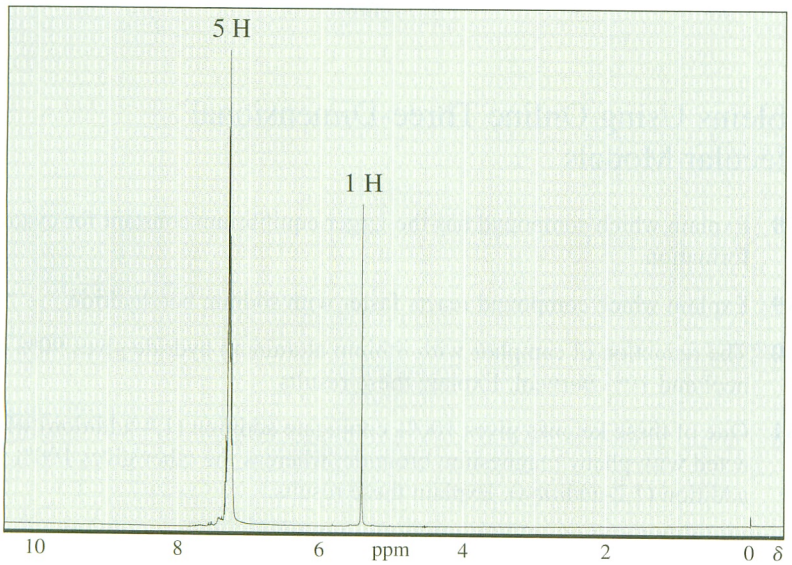
18.54 A student set out to synthesize the following compound in the laboratory. When the compound was isolated, its IR spectrum did not show a strong absorption band in the region of 1730 cm^{-1}. Was the synthesis unsuccessful? Explain.



18.55 The reaction of 2 moles of benzaldehyde with 1 mole of hydrazine gives a product with the formula $C_{14}H_{12}N_2$. This compound shows only five absorptions in its ^{13}C-NMR spectrum. Suggest a structure for the product of this reaction.

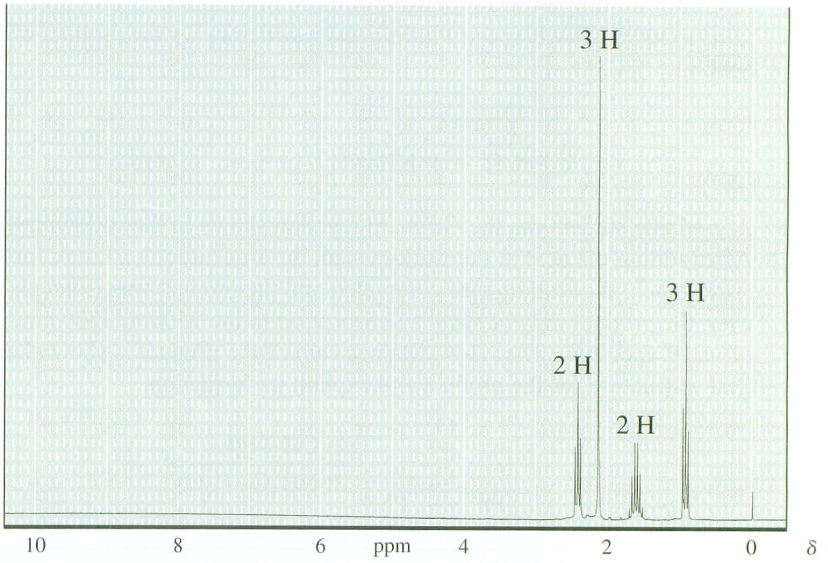
18.56 A graduate student ran the Grignard reaction shown in the following equation. After adding the acid in the workup step, the student took a break for lunch. After lunch, the workup was completed and the product was isolated. However, the product did not show an absorption in the 3500 to 3200 cm^{-1} region of its IR spectrum. The ^1H-NMR spectrum of the product is shown here. Suggest a structure for the product and explain its formation.





18.57 A graduate student ran the Grignard reaction shown in the following equation. The student was unaware that the flask that was used for the reaction was contaminated with some copper(I) salt. The product that was isolated had no absorption in the 3500 to 3200 cm^{-1} region of its IR spectrum but did have a strong absorption near 1715 cm^{-1}. The ^1H-NMR spectrum of the product is shown here. Suggest a structure for this compound.

$$CH_2{=}CHCCH_3 \xrightarrow[2)\ NH_4Cl,\ H_2O]{1)\ CH_3MgI} C_5H_{10}O$$



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Problems Using Online Three-Dimensional Molecular Models

18.58 Explain which compound has the larger equilibrium constant for cyanohydrin formation.

18.59 Explain which compound reacts faster with sodium borohydride.

18.60 The reduction of camphor with lithium aluminum hydride gives 90% isoborneol and 10% borneol. Explain these results.

18.61 One of these ketones gives 100% conjugate addition (1,4-addition) when reacted with phenylmagnesium bromide, whereas the other gives 100% normal addition (1,2-addition). Explain these results.